Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 1963

Population-based studies in Myelodysplastic syndromes

Prognostic scores, socioeconomic status, and therapy-related disease

DANIEL MORENO BERGGREN

ACTA UNIVERSITATIS
UPSALIENSIS
2023

ISSN 1651-6206
ISBN 978-91-513-1858-5
urn:nbn:se:uu:diva-508646

UPPSALA
UNIVERSITET

Dissertation presented at Uppsala University to be publicly examined in H:son Holmdahlsalen, Uppsala University Hospital, Entrance 100, Uppsala, Friday, 22 September 2023 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Honorary Visiting Professor David Bowen (University of York, Storbritannien).

Abstract

Moreno Berggren, D. 2023. Population-based studies in Myelodysplastic syndromes. Prognostic scores, socioeconomic status, and therapy-related disease. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1963. 71 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1858-5.

The aim of this thesis was to expand the epidemiological knowledge of the haematological malignancy MDS and the related condition chronic myelomonocytic leukaemia (CMML). Using nationwide registers, the papers in this thesis address aspects of prognostication, comorbidity, socioeconomic status, and therapy-related disease, using a population-based approach.

In paper I we validated the prognostic scoring systems WPSS, IPSS, and IPSS-R in a cohort of 1329 MDS patients. IPSS-R was the most effective scoring system, with the highest C-index of 0.74. The scoring systems were equally effective for therapy-related MDS (t-MDS) as they were for de novo MDS.

In paper II we validated the scoring systems, IPSS-R, CPSS, MDAPS, and Mayo score and the comorbidity indices CCI, HCT-CI, and MDS-CI in a cohort of 337 patients with CMML. We concluded that CPSS is the most powerful scoring system. Among comorbidity indices, the CCI gave the most prognostic information. There was a strikingly high prevalence of autoimmune conditions affecting 25% of patients.

In paper III we studied the effect of socioeconomic status in a cohort of 2945 patients with MDS. When adjusting for known prognostic factors, mortality was 50% higher in patients with the lowest income compared to those with the highest income and 40% higher among patients with the shortest education compared to those with the longest. Further, a lower socioeconomic status was associated with a reduced probability of receiving effective treatment and with a lower probability of a cytogenetic evaluation at diagnosis.

In paper IV we studied t-MDS in a cohort of 2705 patients with MDS, of whom 16% had t-MDS. Patients with t-MDS had a shorter median survival as compared to de novo MDS (15.8 months versus 31.1 months). Previous treatment with either chemotherapy alone or in combination with radiation was associated with a shorter survival than treatment with radiation only. Having a non-malignant disease or a solid tumour as a primary disease was associated with a longer survival, compared with those with a haematological malignancy. IPSS-R and the WHO classification were effective in predicting survival in most subgroups of t-MDS. The t-MDS subgroup treated with radiation only was similar to patients with de novo MDS and should be regarded as having de novo MDS regarding prognostication and treatment.

In summary, the findings in this thesis provide evidence for how to improve prognostication and expand knowledge on the patient and disease-specific characteristics leading to the diverse outcomes in MDS and CMML.

Keywords: Myelodysplastic syndromes, Chronic myelomonocytic leukaemia, Prognostication, Comorbidity, Therapy-related disease, Real-world data, Population-based studies

Daniel Moreno Berggren, Department of Medical Sciences, Haematology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-1858-5
URN urn:nbn:se:uu:diva-508646 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-508646)

To Theo and Julia

The obvious is sometimes false; the unexpected is sometimes true.
— Carl Sagan, who suffered from MDS

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Moreno Berggren D, Folkvaljon Y, Engvall M, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. *British journal of haematology*. 2018;181(5):614-627. doi:10.1111/bjh.15243

II. Moreno Berggren D, Kjellander M, Backlund E, et al. Prognostic scoring systems and comorbidities in chronic myelomonocytic leukaemia: a nationwide population-based study. *British journal of haematology*. 2021;192(3):474-483. doi:10.1111/bjh.16790

III. Larfors G, Moreno Berggren D, Garelius H, et al. Income, education and their impact on treatments and survival in patients with myelodysplastic syndromes. *European journal of haematology*. 2021;107(2):219-228. doi:10.1111/ejh.13641

IV. Moreno Berggren D, Garelius H, Willner Hjelm P, et al. Therapy-related MDS dissected based on primary disease and treatment-a nationwide perspective. *Leukemia*. 2023;37(5):1103-1112. doi:10.1038/s41375-023-01864-6

Contents

Abbreviations

AML	Acute myeloid leukaemia
AZA	Azacitidine
CCI	Charlson comorbidity index
CCUS	Clonal cytopenia of undetermined significance
CDR	Swedish Cause of Death register
CHIP	Clonal haematopoiesis of indeterminate potential
CI	Confidence interval
CMML	Chronic myelomonocytic leukaemia
CPSS	CMML-specific prognostic scoring system
EPO	Erythropoietin
FAB	French-American-British co-operative group
Hb	Haemoglobin
HCT-CI	Hematopoietic Cell Transplantation-Comorbidity Index
hMDS	Hypoplastic MDS
HMA	Hypomethylating agents
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
ICC	International Consensus Classification
ICD	International Classification of Diseases
ICUS	Idiopathic cytopenia of undetermined significance
IPSS	International Prognostic Scoring System
IPSS-M	Molecular International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
LDH	Lactate dehydrogenase
MDAPS	MD Anderson Prognostic Scoring System
MD-CMML	Myelodysplastic-CMML
MDS	Myelodysplastic syndromes
MDS-CI	Myelodysplastic syndrome-specific comorbidity index
MDS/MPN	Myelodysplastic/myeloproliferative neoplasms
MP-CMML	Myeloproliferative-CMML
MPN	Myeloproliferative neoplasms
NGS	Next generation sequencing
NPR	Swedish National Patient Register
NR	Not reached
OR	Odds ratio
RA	Refractory anaemia

RAEB	RA with excess blasts
RARS	RA with ring sideroblasts
RBC	Red blood cell
RCC	Regional Cancer Centre
SCB	Statistics Sweden
SCR	Swedish Cancer Register
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
SMDSR	Swedish MDS register
t-AML	Therapy-related AML
t-CMML	Therapy-related CMML
t-MDS	Therapy related MDS
t-MN	Therapy-related myeloid neoplasms
VAF	Variant allele frequency
WHO	World Health Organisation
WPSS	WHO Classification-based Prognostic Scoring System
WBC	White blood cell count

Background

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal hematopoietic stem cell disorders, characterised by dysplastic and ineffective haematopoiesis leading to cytopenias and the risk of transformation to acute myeloid leukaemia (AML). The recognition of MDS, understanding of its epidemiology, and the development of treatments for MDS has lagged behind that of other haematological malignancies. Despite their poor prognosis, MDS were formally classified as cancers as late as 2001 by the World Health Organisation (WHO). MDS have a substantial and negative effect on patients' lives, and symptoms such as fatigue, pain, dyspnoea, anxiety, and stress are common[1-3]. Furthermore, the cost to society for the care of MDS-patients can be substantial[4,5].

Over the past few decades, there has been a revolution in the development of new treatments for many haematological malignancies, but this revolution is yet to come for MDS. On the positive side, there is a growing understanding of the pathogenesis and biology of MDS, prognostication and risk stratification have improved, and clinical trials are becoming more frequent. The following pages offer a short overview of several aspects of these fascinating diseases.

Epidemiology — characterising the beast is a prerequisite to taming it

The yearly incidence of MDS is reported to be approximately 3–5 per 100,000 inhabitants[6-11] and the median age at diagnosis is around 75 years[9]. Incidence increases sharply with age, from 0.1/100,000 in the age group 1–29 years to 61.5/100,000 for patients 85 years and older (Figure 1). Incidence rates are higher among males than females, with a male/female ratio of around 1.7[8,11]. This male/female ratio increases with age[11,12]. Finding the true incidence of MDS has been difficult. Incidence data from cancer registers might not represent true incidence rates, as underdiagnosis is a potential problem. Asymptomatic patients might never be diagnosed, and a full diagnostic work up might not be performed for all elderly patients with unexplained anaemia[13,14]. Using data from the Düsseldorf MDS Registry from 1996-2005, *Neukirchen et al.* reported an age-standardised prevalence of 7 per 100,000 persons[15]. A recent

Danish study showed a slight increase in the age-standardised incidence ratio from 5.3 per 100,000 in 2010 to 6.4 per 100,000 in 2019[16]. With a growing elderly population, the prevalence of MDS is expected to increase, and hopefully, improved treatments will also add to this increase by prolonging survival.

The prognosis varies considerably for individual patients, with survival ranging from months to decades. The 5-year overall survival (OS) is reported to be 21%–33%[9,12,16]. The reported survival will be affected by the fact that MDS onset is insidious. Routine blood count measurements in asymptomatic patients, delayed diagnosis in patients with comorbidities that also might cause anaemia, and the patient's own tendency to seek medical care will influence the timing of diagnosis and subsequently, survival[11,17]. Approximately 30% of MDS patients transform to AML, the median latency time is 1–1.5 years, and if progression to AML occurs, prognosis is dismal with a survival of around 6–12 months[18,19].

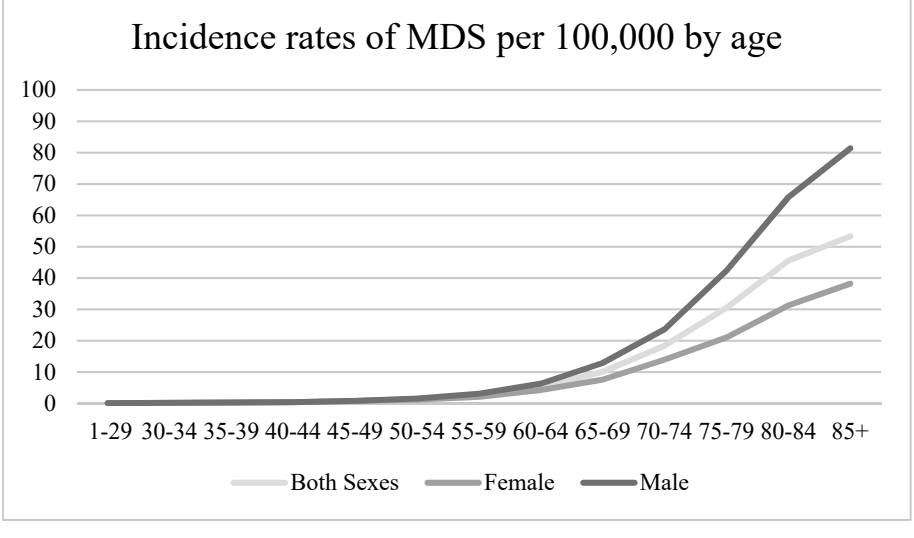

Figure 1. Incidence of MDS in relation to age at diagnosis. *Data from the SEER database 2015–2019. SEER explorer updated September 1, 2022.*

The Swedish MDS register — a national quality registry and a tool for research

All studies in this thesis have a population-based approach, and basic data for all studies was gathered from the Swedish MDS register (SMDSR). Sweden has a long tradition of keeping healthcare quality registries, the first of which, initiated in 1975, concerned knee arthroplasty. Today Sweden has more than

100 National Health Care registries funded by the Swedish Association of Local Authorities and Regions. They are mainly used to monitor and improve the quality of healthcare, and are an excellent research tool. Population-based registers with high coverage have the advantage of including not only a representative sample, but virtually the total population. Studies based on these registers have a higher generalisability than clinical trials and data from more selected cohorts such as academic centres.

The SMDSR is one of eight registers constituting the larger blood cancer register, and was started in 2009 by the Swedish section of the Nordic MDS group and the Swedish Society of Haematology. It has nationwide coverage for the Swedish population of 10.5 million people and includes patients aged 16 or over (except 16-19 year olds diagnosed at paediatric clinics) diagnosed with MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and currently includes more than 5000 patients[6]. All hospitals in Sweden diagnosing patients with MDS report to the register. A total of 70 hospitals have so far included patients, with 46% of patients having been reported from university hospitals[6] (see Figure 2 for the geographical distribution of the contributing sites). The register is supported by the Swedish Association of Local Authorities and Regions and managed in collaboration with the Regional Cancer Centre (RCC) Mellansverige. Coverage, as measured against the Swedish Cancer Register (SCR) is excellent, but there is a significant time lag between diagnosis and inclusion in the register. At the end of 2022 the coverage was 98% for the period 2009–2016, 89% for the period 2017–2020, but only 68% for 2021[6]. If a MDS patient is reported to the SCR but not to the SMDSR, the RCCs actively request clinicians to report the case to the SMDSR.

Data in the register include date of diagnosis, age, gender, WHO category, laboratory parameters, transfusions dependency, antecedent haematological disease, previous cytotoxic treatment, and diagnostic procedures including bone marrow morphology and cytogenetics. Data on mutations have been collected since 2020. Data are collected at diagnosis, and at 1, 3, 6 and 9 years after diagnosis. The studies in this thesis will be the first ones based on the SMDSR.

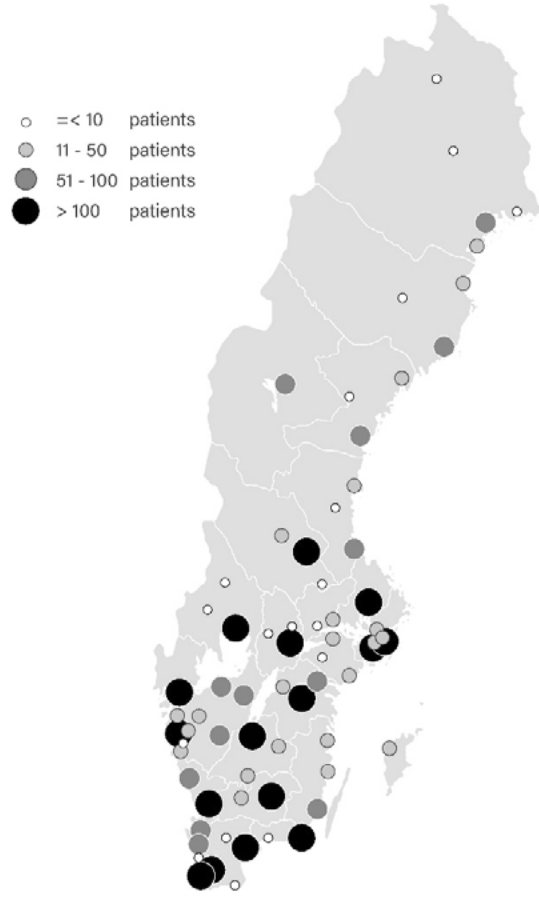

Figure 2: The geographical distribution of the contributing sites in SMDSR 2009–2021.

Pathogenesis — an expanding field with many players

The current understanding of the pathogenesis of MDS is that accumulation of genetic damages in hematopoietic stem cells leads to clonal evolution which, through additional mutations, epigenetic alterations, abnormal bone marrow microenvironment and inflammation leads to malignant transformation.

Genetics

The first mutations provide an advantage at the stem cell level but a disadvantage for the hematopoietic precursors leading to premature intramedullary death of myeloid precursors[20]. This initiating mutation gives rise to a clone,

resulting in clonal haematopoiesis. Clonal haematopoiesis is strongly associated with age, and is seen in around 10% of people older than 70 years, although approximations like this will be highly dependent on the sensitivity of the sequencing technique used[21,22]. It is not well understood why some persons with clonal haematopoiesis develop myeloid diseases while most do not. During recent years, substantial work has been done identifying the driver mutations of MDS, some mutations are highly recurrent, but the majority of them are rare[23-26]. Mutations in splicing factors such as *SF3B1*, *SRSF2*, and *U2AF* are the most common type of mutations and they are suggested to occur early on in the disease development[23,27]. Genes that control epigenetic regulations, such as *TET2, ASXL1*, *DNMT3A*, *IDH1*, *IDH2* and *EZH2* are the second-most common type of mutation, and are also considered to occur early in MDS development[23]. Loss-of-function of genes in the cohesion complex such as *STAG2* are the third-most common type. *TP53* is probably the most well-known tumour suppressor gene and it is frequently mutated in MDS[28]. Mutations in genes involved in cell signalling, such as *NRAS,* are less common in MDS as compared to other myeloid malignancies.

Approximately 50% of MDS patients have chromosomal aberrations[29-31]. Balanced abnormalities such as translocations, inversions, and insertions are often found in AML, but are uncommon in MDS. Most chromosomal aberrations are unbalanced, resulting in the loss or gain of a large amount of genetic material. Deletion of (5q), chromosome 7 abnormalities (monosomy 7 or deletion of (7q)) and trisomy 8 are the most common aberrations[29]. Some patients have a complex karyotype (≥3 aberrations), and this is associated with a dismal prognosis.

Age, inflammation, and the bone marrow niche

There are likely several causes contributing to genetic damage. Age-related accumulation of mutations is probably a predominant one[32]. Additionally, shortening of telomeres is frequently observed, and is associated with both age and exposures to toxic substances[33,34]. Epidemiological studies have shown associations between MDS and autoimmune conditions[35-37]. This has led to the theory that chronic inflammation is another source of genetic damage and may promote MDS. Genetic damage is thought to lead to the activation of immune signalling and secretion of cytokines, such as TNF-α, which leads to increased apoptosis of myeloid progenitor cells in the bone marrow, resulting in cytopenias, the hallmark of MDS[38,39] Aberrant regulation of the immune system and low-grade inflammation gives MDS cells a growth advantage, resulting in a clonal expansion which drives MDS progression[40]. The bone marrow microenvironment, or 'niche', has received more scientific attention over the last few years, and aberrations in the bone marrow microenvironment likely play a role in all steps of MDS development[41].

Germline predisposition

The majority of the above-described genetic alterations are somatic, occurring at some point in a person's life. But over the last decade it has been recognised that hereditary MDS is more common than had been previously thought. Current estimates suggest that about 5%–15% of patients with MDS have germline mutations in cancer susceptibility genes[42,43]. Some mutations are associated with a specific syndrome, such as Shwachman-Diamond syndrome, Diamond-Blackfan anaemia, or telomere disorders, and these are often diagnosed in childhood. But in other mutations such as *RUNX1*[44], *GATA2*[45], and *DDX41*[46], MDS can be the first presentation. Suspicion of a germline mutation might be raised in patients who develop MDS at a young age, have a family history of myeloid disease, or have specific mutations with a variant allele frequency (VAF) suggesting a germline mutation. Identifying a hereditary mutation will have implications for family members, and for donor selection in the case of hematopoietic stem cell transplantation (HSCT).

Risk factors

Lifestyle has a limited effect on the risk of MDS. Smoking and exposure to toxic agents such as benzene (which is found in tobacco smoke) are the two most often described exposures that increase the risk of MDS[47,48]. Exposure to cytotoxic agents and radiation used to treat malignant and non-malignant diseases increases the risk of MDS[49,50]. Therapy-related MDS (t-MDS) will be discussed in a separate section.

In conclusion, the pathogenesis of MDS is complex and involves interplay between the genetic alterations of clonal haematopoiesis, inflammatory signalling, immune dysregulation, and the bone marrow microenvironment.

Diagnosis and classification — a moving target

Diagnostic work-up

Patients with MDS may present with symptoms of cytopenias such as fatigue, dyspnoea on exertion, bleeding, or infections. Others present without symptoms but with isolated or combined cytopenias where anaemia usually is predominant[51,52]. Diagnosis of MDS depends on clinical evidence of ineffective haematopoiesis, with cytopenias in peripheral blood, and finding of dysplasia in the bone marrow. Integration of peripheral blood values, bone marrow morphology, cytogenetics, and mutational screening with next generation sequencing (NGS) form the basis for diagnosing MDS[53]. At least 10% dysplastic cells in any hematopoietic lineage is required and cytopenia is defined as: haemoglobin (Hb) <100 g/L; platelet count $<100x10^9$/L; and an absolute neutrophil count of $<1.8x10^9$/L[54]. Cytogenetic abnormalities are present in around

50% of patients, and have an important impact on prognosis[29]. Patients with deletions of the long arm of chromosome 5, del(5q), alone or with one additional abnormality, are defined as a specific subtype, with a favourable prognosis[55]. Some cytogenetic abnormalities such as del(5q) and monosomy 7 are considered MDS-defining, even in the absence of significant marrow dysplasia[56]. Over 90% of patients with MDS have mutations in recurrently-mutated myeloid genes, and introducing NGS has significantly improved the diagnostic work-up. Some specific mutations, such as mutations in *SF3B1*[57] and *TP53* define subgroups of MDS in the most recent classification. Patients with biallelic *TP53* mutations constitute a specific subgroup with an especially poor prognosis[28]. MDS patients with *TP53* mutations and an increase in blasts have an equally poor prognosis as AML with a mutated *TP53,* and they are in the updated WHO classification considered a distinct disease entity[58,59].

Classification

In the early 1900s, reports of patients with cytopenia, bone marrow dysplasia and development of AML appeared in the literature, and these conditions were described as 'preleukemia'[60]. Conditions with anaemia that did not respond to vitamin supplements, so-called 'refractory anaemia', were also described. A link between these two conditions was established during the 1950s, but the nomenclature was confusing and clear definitions were lacking until MDS was defined in 1982 by the French–American–British (FAB) co-operative group[61]. Five MDS were described: refractory anaemia (RA), RA with ring sideroblasts (RARS), RA with excess blasts (RAEB), chronic myelomonocytic leukaemia (CMML) and RAEB in transformation. The WHO extended and updated the classification of MDS in 2001[62] with a revision in 2008[63] and again in 2016[54]. The changes of the classification of MDS are described in Figure 3. In 2022, two revisions of the WHO 2016 were presented, one as the fifth edition of the WHO classification[64] and one as the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias[59]. In WHO 2022, the term *myelodysplastic neoplasms* was introduced, replacing myelodysplastic syndromes but retaining the abbreviation MDS[64]. The WHO classification used in this thesis is the one from 2016, which is presented in table 1.

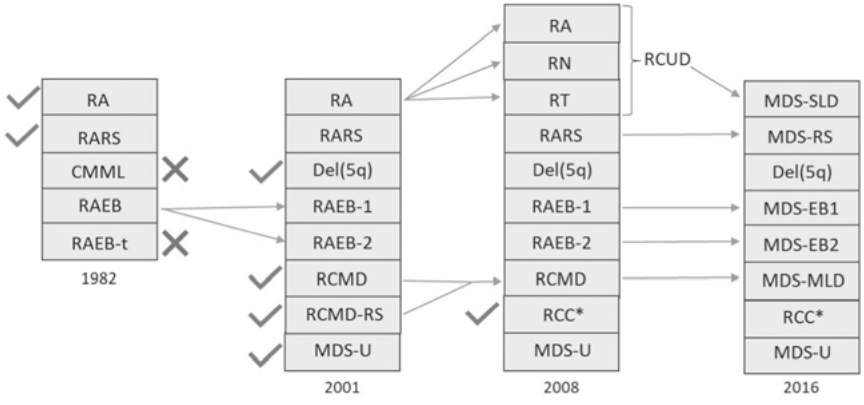

Figure 3. The evolving classification of MDS from 1982–2016. Adapted from *Zeidan et al. 2019*[12]. Reprinted with kind permission from Elsevier.

Table 1: 2016 WHO classification of MDS					
Disease	**Dysplastic lineages**	**Cyto-penias**	**Ring sideroblasts**	**Blasts**	**Cytogenetics**
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	Blasts <5%, PB <1%	Any, unless fulfills criteria for del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%	Any, unless fulfills criteria for del(5q)
MDS with ring sideroblasts (MDS-RS)					
with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%	Any, unless fulfills criteria for del(5q)
with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%	Any, unless fulfills criteria for del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%	del(5q) alone or one abnormality except −7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19%	Any
MDS,unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

Adapted from *Arber et al*. 2016[54]. † If *SF3B1* mutation is present, § Cases with ≥5% ring sideroblasts by definition have significant erythroid dysplasia and are classified as MDS-RS-SLD. BM=Bone marrow, PB=Peripheral blood.

Overlapping conditions

Several conditions have features that overlap between MDS and myeloproliferative neoplasms (MPN), including CMML, atypical chronic myeloid leukaemia, MDS/MPN with ring sideroblasts and thrombocytosis, and juvenile myelomonocytic leukaemia. Of these MDS/MPNs, CMML is by far the most common one and will be described in detail in a later section.

Most patients with MDS have a normo- or hypercellular bone marrow, but in 10%–20% it is hypo-cellular, i.e. hypoplastic MDS (hMDS), leading to a diagnostic overlap with aplastic anaemia (AA)[65,66]. Patients with hMDS share some features with patients with AA, and a subset of patients with hMDS respond well to immunosuppressive treatments[67]. The spectrum of overlapping haematological diseases is presented in Figure 4.

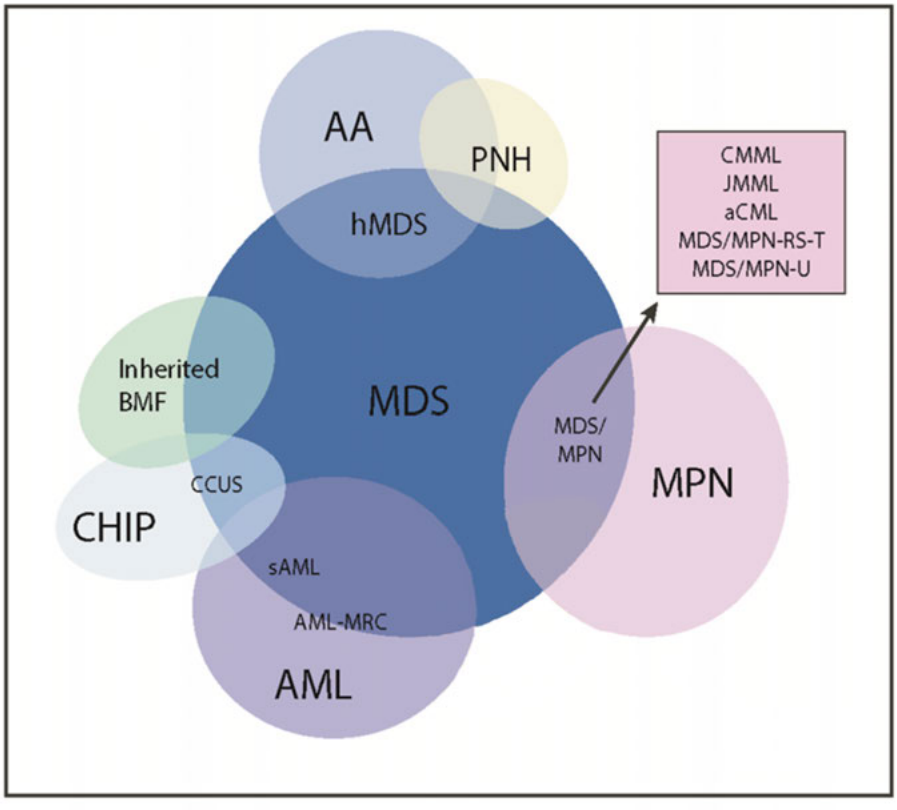

Figure 4. The main conditions overlapping MDS. Adapted from *Tanka et al.* 2019[65]. Reprinted with kind permission from Elsevier. PNH=Paroxysmal nocturnal haemoglobinuria, BMF= Bone Marrow failure.

Over the last decade the understanding that myeloid neoplasms in many cases arise from clonal haematopoiesis has proposed a timeline of a multistep clonal evolution, from clonal haematopoiesis of indeterminate potential (CHIP) to

MDS and ultimately to secondary AML. Individuals with CHIP have somatic mutations in genes associated with myeloid malignancies without other signs of haematological disease[68]. These individuals have an increased risk of developing myeloid malignancies, and this relationship parallels that of monoclonal gammopathy of undetermined significance and multiple myeloma. Cytopenias without dysplasia or cytogenetic abnormalities defining MDS is called idiopathic cytopenia of undetermined significance (ICUS)[69,70]. If patients with idiopathic cytopenia have a mutation in a gene known to be mutated in myeloid malignancies, the condition is called clonal cytopenia of undetermined significance (CCUS)[71]. Patients with CCUS have a high risk of developing myeloid malignancies and some specific mutations and combinations of mutations convey an especially high risk, particularly if the mutation has a high VAF[72]. The diagnostic boundary between CCUS and MDS is not always clear-cut, and these conditions could often be considered different stages of the same pathological condition. On the other side of the spectrum, the same is true for the boundary between MDS with high blasts and secondary AML. An overview of these conditions is presented in Figure 5.

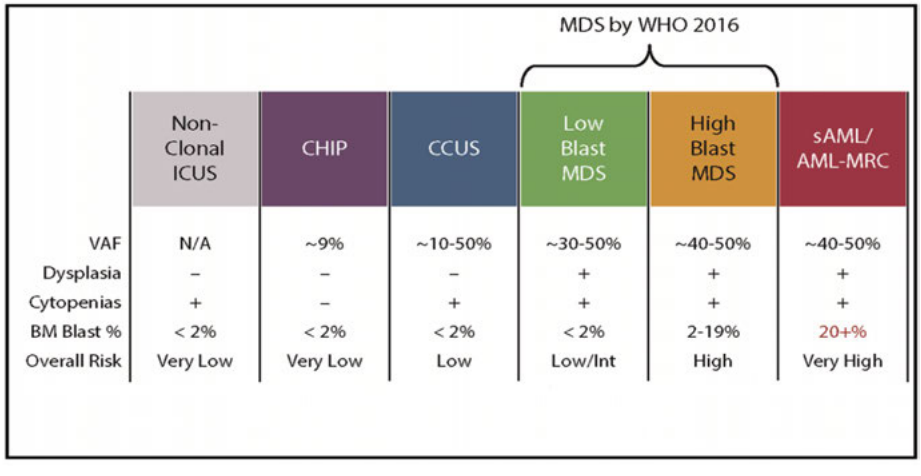

Figure 5. Diagnostic boundaries of conditions with clonal haematopoiesis. Adapted from *Tanka et al.* 2019[65]. Reprinted with kind permission from Elsevier. VAF=Variant allele frequency

Prognostication — continuous improvements but still some way to go

Since the clinical outcomes of patients with MDS are highly variable, prognostic scoring systems are important tools in estimating survival and guiding clinicians in individualising treatment. The International Prognostic Scoring System (IPSS) has been the standard risk stratification tool for patients with MDS since 1997[73]. From an analysis of around 800 patients with all FAB subgroups (excluding proliferative CMML), the IPSS defined four risk groups based on the percentage of bone marrow blasts, number of cytopenias, and cytogenetics. Using IPSS, patients are often categorised as having "low risk MDS" (low and intermediate-1) or "high risk MDS" (intermediate-2 and high-risk groups) in clinical practice. In 2007, the WHO Classification-based Prognostic Scoring System (WPSS) was published. It classifies patients into five risk groups based on: WHO morphologic categorisation of MDS, transfusion dependency, and the IPSS cytogenetic classification[74]. Based on criticism for using a subjective variable such as transfusion dependency as a measure of severe anaemia [75], a revised WPSS with sex specific Hb-levels has been introduced[76].

In 2012 a revision of the IPSS: the Revised International Prognostic Scoring System (IPSS-R) was introduced[77]. This refined scoring system was based on a large cohort of around 7000 patients. The updates were the integration of the "New Comprehensive Cytogenetic Scoring System"[30] which included more categories of chromosomal aberrations, a higher scoring weight given to cytogenetic abnormalities, a decreased weight to elevated bone marrow blasts, new cut-off limits for marrow blast percentage values and a replacement of the number of cytopenias with the depth of cytopenias. The number of risk groups increased from four to five. A cut of IPSS-R score of <3.5 can be used to distinguish lower and higher risk MDS[78].

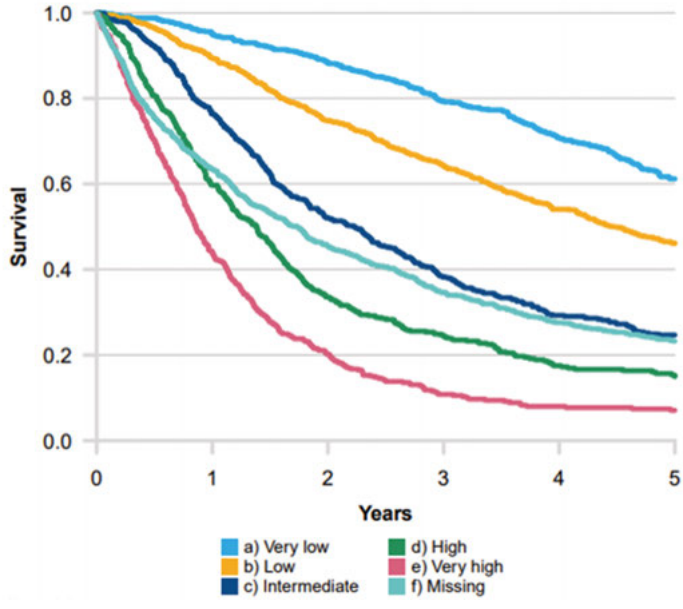

Figure 6. Survival according to IPSS-R groups from the SMDSR 2009-2021. Adapted from *Myelodysplastiskt syndrom (MDS) Rapport för diagnosår 2009–2021.*

The original cohorts for IPSS, IPSS-R and WPSS were newly-diagnosed patients excluding t-MDS and patients receiving disease-modifying treatments. They were developed with OS and AML-transformation as end-points. There are also several reports indicating that IPSS-R can adequately risk stratify patients with various treatments including HSCT[79-81]. IPSS-R and other scores have also been shown to have prognostic utility in t-MDS[82-84]. The survival according to different IPSS-R groups in the Swedish MDS-register 2009–2021 is depicted in Figure 6. Several large studies have shown that specific mutations and the number of mutations have prognostic importance in addition to the clinical variables from IPSS and IPSS-R[23,85-87].

In 2022, a molecular prognostic scoring system, the IPSS-M, was published[88]. The scoring system was created after international efforts to construct a discovery cohort of 2957 patients, of whom approximately 25% were Swedish. Patients with secondary/therapy-related MDS (8.1%) and MDS/MPN with a white blood cell count less than 13×10^9 (12.8%) were included. The IPSS-M has been externally validated and has been shown to increase the prognostic discrimination when compared to IPSS-R[89]. The IPSS-M uses blood cell counts, blasts, the cytogenetic categories from IPSS-R, and mutational data. The model yields a virtually unique score for each patient, with the scores divided in to six risk categories. A substantial difference between IPSS-R and IPSS-M is that IPSS-M includes patients (30%) treated with dis-

ease-modifying drugs and HSCT. Since the studies in this thesis are retrospective, lacking mutational data, IPSS-R was mainly used to risk-classify patients.

As MDS mainly affects the elderly, age and comorbidity can influence prognosis. Age has an independent effect on survival in low-risk MDS, but not in high-risk MDS[73,74,90]. In high-risk patients, age has an indirect effect on survival by limiting their eligibility for intensive treatments[90]. Patients with MDS are reported to have a high prevalence of comorbid conditions[91,92]. Several comorbidity indices have been validated for MDS, including the Charlson comorbidity index (CCI), the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) and the myelodysplastic syndrome-specific comorbidity index (MDS-CI)[91-94]. In addition to comorbidity, assessment of frailty has been shown to improve prognostication in MDS[95].

Treatment – a short menu in need of expansion

The only potential curative treatment for MDS is HSCT, which should in general be considered for higher risk patients under the age of 70–75 years without significant comorbidity[96,97]. In the SMDSR, 14% of patients younger than 75 years are reported to be planned for HSCT at diagnosis[6].

Patients with low-risk MDS and asymptomatic cytopenia do not require any treatment, and should be monitored regularly. This might also be an option for all unfit patients with a short life expectancy. In the SMDSR, 42% of patients are RBC transfusion-dependent at diagnosis, making anaemia one of the major challenges in MDS[6].

Erythropoietin (EPO): EPO is the first-line treatment for all symptomatic anaemic patients with low-risk MDS[98,99]. Overall response rate is reported to be around 40–60% and the median duration of response is 20–24 months. Responses are better in patients without, or with a low transfusion burden and a low serum EPO[100-102]. EPO reduces the need for transfusions, improves quality of life, and may also improve survival[101-104].

Lenalidomide: Lenalidomide is an immunomodulatory agent developed from thalidomide. It is mainly used for low-risk MDS patients with del(5q) who have failed EPO or have a low likelihood of response to EPO[98,99]. In an open-label single-centre trial, MDS patients with symptomatic anaemia or transfusion dependency, were treated with lenalidomide. Overall, 56 % of patients responded, with high percentages of transfusion independence and cytogenetic responses seen in patients with del(5q)[105]. Subsequent studies established lenalidomide as a cornerstone in the treatment of lower risk MDS with del(5q)[106-108].

Some patients might not respond to EPO or lenalidomide and many will lose their response with time. These patients will depend on regular RBC transfusions and some of these will need iron chelation as part of their supportive care[98,109].

Thrombopoietin receptor agonists: Romiplostim and eltrombopag are used to treat thrombocytopenia in immune thrombocytopenia, and aplastic anaemia. They increase platelet counts and reduce bleedings in low-risk MDS[110,111]. Initial reports raised a concern of increased risk of progression to AML[112] but this has not been confirmed in long-term follow-up studies, at least not for low-risk MDS[113,114]. The combination of azacitidine (AZA) and eltrombopag in high-risk MDS resulted in worse platelet recovery and with a trend toward increased leukemic progression[115].

Immunosuppressive treatment: Treatments such as anti-thymocyte globulin, corticosteroids, and cyclosporine are used for some low-risk MDS patients. The current practice is to consider anti-thymocyte globulin with or without cyclosporine as treatment for younger patients with low risk MDS, a hypo-cellular marrow without excess of blasts, and a normal karyotype[98,99,116].

Treatments for high-risk MDS: As mentioned earlier, high-risk patients should be considered for HSCT. The role of cytoreductive chemotherapy before HSCT is debated, but it is usually given to patients with more than 10% blasts[97,99]. The first-line treatment for most high risk MDS are the hypomethylating agents (HMA), AZA, or decitabine, with AZA being the most frequently used in Europe. In a phase III study comparing AZA to conventional care, the OS improved from 15 to 24 months[117]. Responses are often late, and the bone marrow is usually evaluated after 6 cycles. The median response duration is around one year[116]. With the introduction of HMAs, the role of induction chemotherapy is mainly as a possible bridge to transplantation, although AZA is also used for this purpose[118].

Future perspectives: There is a great need for new effective treatments for MDS. Many patients with low-risk MDS fail first- and second-line treatments and are forced to undergo regular transfusions. Most high-risk MDS patients are not eligible for HSCT, and only few patients achieve long-lasting remissions with HMAs. For low-risk MDS, hypoxia-inducible factors such as roxadustat and telomerase inhibitors such as imetelstat are promising therapies[116]. The erythroid maturation agent luspatercept reduces the severity of anaemia in low-risk MDS, especially in MDS-RS. It is approved in both Europe and America, but is not currently available in Sweden[119,120]. For high-risk MDS, combinations with HMAs are being studied. In AML, the BCL2 inhibitor venetoclax in combination with HMAs has gained widespread use,[121] and this combination also shows encouraging results in high-risk MDS[122,123]. Also

in AML, targeted treatments such as IDH-inhibitors and FLT3-inhibitors have been introduced in the last few years and they might be an option for the small number of patients with high-risk MDS with these specific mutations[116].

CMML — time to cut the cord from MDS

The reported yearly incidence of CMML is 0.3–0.7 per 100,000 inhabitants and the age distribution is similar to that of MDS[9,124,125]. Survival ranges from months to decades with a five-year OS reported to be 13–23%[9,125]. The 5-year cumulative probability of progression to AML is reported to be 21–29%[126,127].

Diagnosis

The clinical presentation of CMML is heterogeneous, varying from a MDS-like disease with cytopenia, to a proliferative disease with leucocytosis, splenomegaly, and other types of extramedullary manifestations[128,129]. In the 2016 WHO classification, CMML is defined by persistent (>3 months) peripheral monocytosis (>1x 10^9/L), accounting for more than 10% of the white blood cell count[128,130]. The criteria for other MPN should not be met and there should not be a prior history of these conditions. Moreover, in patients with suspected CMML and eosinophilia, it is important to exclude rearrangement of the platelet-derived growth factor receptor, fibroblast growth factor 1, and PCM-JAK2 fusions. There should be less than 20% myeloblasts and promonocytes in peripheral blood or bone marrow since a higher proportion is diagnostic for AML. Myeloid dysplasia is a common finding on bone marrow examination, but it is not obligatory if the other criterias are met. Acquired cytogenetic or molecular abnormalities (*TET2*, *ASXL1*, *SRSF2* or *SETBP1*) can support the diagnosis. To confirm the diagnosis, all non-clonal and inflammatory causes of monocytosis should be excluded. This last point can make diagnosing CMML quite a challenge. During recent years, flow cytometry has proven to be an important method in distinguishing the monocytosis of CMML from reactive monocytosis. A high fraction of classical monocytes is a good marker of true CMML[131,132].

Classification

In 1976 CMML was recognised as a subset of MDS by the French–American–British (FAB) Group[133], and later a dysplastic subtype (MD-CMML) and a proliferative subtype (MP-CMML) were described based on a white blood cell count (WBC) of ≤13x10^9/L and >13x10^9/L, respectively[134]. In the WHO classification of 2008, CMML was included in the group of MDS/MPN and subdivided into two groups based on percentage of blasts[56]. The WHO classification of 2016 uses three groups of blast percentage as CMML categories:

CMML-0 (<2% peripheral blast and <5% marrow blast); CMML-1 (2–4% peripheral blasts and/or 5–9% marrow blasts); and CMML-2 (>5% peripheral blasts and 10–19% marrow blasts and/or the presence of Auer rods) [54]. In the WHO classification of 2022, the subgroup of CMML-0 was eliminated[64].

Prognostication

Whereas there is considerable consensus about using IPSS-R and IPSS-M in the prognostication of MDS, there is no consensus regarding prognostic scoring systems for CMML. In the cohorts used to develop IPSS and IPSS-R, there were small proportions of patients with CMML, but patients with MP-CMML were excluded[73,77]. In the IPSS-M, 9.5% of patients had MD-CMML, but again no patients with MP-CMML were included[88]. Unfortunately, no subgroup analysis of CMML-patients has been presented, making the effectiveness of IPSS-M in MD-CMML difficult to assess. Several CMML-specific scoring systems have been developed. The MD Anderson Prognostic Scoring System (MDAPS) includes Hb <12 g/dL, absolute lymphocyte count > 2.5×10^9/L, circulating immature myeloid cells and bone marrow blasts ≥ 10%[126]. The CMML-specific prognostic scoring system (CPSS) includes FAB classification (MD-CMML versus MP-CMML), WHO classification (CMML-1 versus CMML-2), RBC transfusion dependency, and the Spanish cytogenetic risk classification[127,135]. The Mayo score is based on absolute monocyte count > 10×10^9/L, circulating immature myeloid cells, Hb < 10 g/dL and platelet count < 100×10^9/L[136].

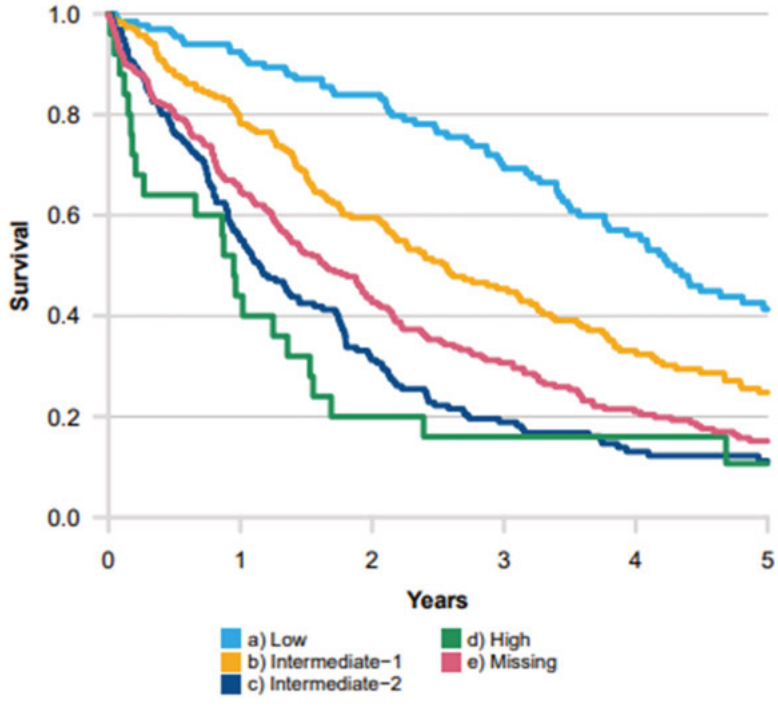

Figure 7. Survival according to CPSS groups from the SMDSR 2009-2021. Adapted from *Myelodysplastiskt syndrom (MDS) Rapport för diagnosår 2009-2021*

Somatic mutations are found in more than 90% of patients with CMML, with mutations in *TET2*, *ASXL1* and *SRSF2* being the most common[137,138]. Specific combinations of mutated genes have been identified as typical for CMML, and selected genes appear to provide useful prognostic information[139,140]. There are now at least three scores that include mutational data. *Groupe Français des Myélodysplasies* prognostic score includes *ASXL1* status together with age, WBC, platelet count and Hb[138]. In the Mayo Molecular Model, *ASXL1* is incorporated into the original Mayo Model [141]. The CPSS has been revised in to the CPSS-molecular, which includes *ASXL1, RUNX1, NRAS,* and *SETBP1* mutations[142].

Pathogenesis and comorbidity

As in MDS, accumulation of mutations in hematopoietic stem cells drives the initiation and progression of CMML[143]. Mutations in *TET2* and *ASXL1* are often early events and these mutations are more common in CMML than in MDS[139,144]. Overall, the mutational spectrum differs between MDS and CMML, and the prognostic impact of specific mutations is also specific for each condition[87,141]. Cytogenetic aberrations are found in about 30% of patients, less than for MDS[145].

Since the age spectra of CMML and MDS are similar, comorbidity is probably common in CMML, but studies of comorbidity in general are lacking and no validation and comparison of comorbidity indices have been performed for CMML[130]. Several studies have focused on autoimmune conditions and they indicate an increased prevalence in patients with CMML[146,147].

Treatment

If clinical studies and new treatments are lacking in MDS, the picture is even darker for CMML. As CMML was considered one of the MDS, patients with CMML have been included in many clinical trials in the context of MDS. Unfortunately, the percentage of patients with CMML has mostly been small and restricted to MD-CMML. In general, the same treatments used for MDS can be considered for CMML. As in MDS, patients with mild cytopenias without any constitutional symptoms usually only require regular monitoring. The only curative treatment is HSCT, and should be considered for all younger patients with higher risk CMML without any major comorbidity[130]. HMAs are approved for the treatment of CMML, in Europe the use is restricted to MD-CMML CMML-2. But in clinical practice it is also considered for selected patients with MP-CMML and CMML-1[130]. Case series and smaller phase 2 studies have demonstrated overall response rates of around 50%[148-151].

Patients with splenomegaly or proliferative symptoms are usually treated with cytoreduction. Larger studies are lacking, but hydroxyurea is the first choice after a study showing improved survival compared to Etoposide[152]. A large retrospective cohort study showed a survival benefit for higher-risk CMML treated with HMAs as compared to hydroxyurea[153]. Hydroxyurea has been compared with HMAs in one randomised phase III study in MP-CMML with no difference in event-free survival[154].

In conclusion, many challenges remain in the diagnosis, prognostication, and treatment of CMML. Every aspect of the disease should be treated as an entity of its own, separated from MDS. The rarity and heterogeneous nature of the condition makes international collaborations essential.

Therapy-related disease — when the remedy is worse than the disease

Therapy-related MDS (t-MDS) following DNA-damaging chemotherapy and/or radiation for a malignant or non-malignant disease, is reported to constitute 10–20% of all MDS cases[155]. In the WHO 2016 classification, t-MDS is included in the entity therapy-related myeloid neoplasms (t-MN), which also includes t-AML and t-MDS/MPN[54]. This separate group was combined with germline predisposition into the group secondary myeloid neoplasms in

the WHO 2022 classification[64]. In the ICC, therapy-related disease is classified the same way as de novo disease, but with the statement "therapy-related" following the diagnosis[59].

As the number of cancer survivors increases, t-MN numbers are also increasing and will probably increase even more in the future[156,157]. Cytotoxic treatment for almost all types of cancer is reported to increase the risk of t-MN[158], but a prior history of breast cancer or haematological malignancies are particularly common primary diseases[156]. Alkylating agents and topoisomerase II inhibitors are considered especially leukemogenic. Alkylating agents are more often associated with t-MDS and a longer latency, while topoisomerase II inhibitors are more frequently associated with t-AML and a shorter latency[156]. Leukemogenesis via ionising radiation is well described in survivors of the atomic bombs[159]. The risk of t-MN after radiation therapy is controversial and conflicting data exists[156]. Earlier studies showed poor outcomes,[49] but more modern studies have suggested a better prognosis and questioned whether modern radiation therapy is indeed a risk factor for t-MN[160,161].

Therapy-related MDS represents one of the most severe complication of cytotoxic treatment and these patients have a substantially shorter OS and more high risk clinical features compared to de novo MDS[49,83]. In the t-MDS group, up to 80% have cytogenetic aberrations, with up to 50% of patients having a complex karyotype, high-risk mutations are also more common in t-MDS than in de novo MDS[82 156].

From an epidemiological point of view, the development of MDS after exposure to chemotherapy or radiation is complex and several possible associations exist.

- **Coincidence:** There might be no causal relation, treatment with cytotoxic agents is quite common in the general population.
- **The primary disease, not its treatment:** The association between treatment for the cancer/autoimmune condition in question and t-MDS might not be driven by exposure to cytotoxic treatment, but rather by the primary disease itself; for example a chronic inflammation driven by the primary malignancy or previous autoimmune condition[35].
- **Genetic predisposition:** There might be a genetic predisposition increasing the risk of both MDS and the previous malignancy/autoimmune condition.
- **Common risk factors:** Environmental exposures or lifestyle factors might increase the risk of both MDS and any previous malignant/autoimmune condition.
- **Direct cytotoxic effect:** The cytotoxic treatment itself causes MDS, representing true therapy-related disease.

For each individual case, causality is difficult to prove, but at the group level, three out of four t-MN are reported to be truly therapy-related[158]. The current understanding of the pathogenesis of t-MN is that cytotoxic treatment leads to a competitive advantage for pre-existing clonal haematopoiesis[162-165]. These clones expand and induce genetic instability, promoting the development of subsequent mutations, eventually leading to t-MN. In addition; the cytotoxic treatment might induce new mutations. Effects on the bone marrow niche and the immune system are also players in the complex pathogenesis of t-MN[166]. There are still substantial knowledge gaps regarding t-MN, but results from the last few years will hopefully provide strategies to reduce this dreaded complication of cytotoxic treatment.

Socioeconomic factors affecting outcome — it´s a rich man's world

Socioeconomic factors such as income and education are well known to affect health outcomes, and are often combined into the term socioeconomic status (SES). Some of the differences in morbidity and mortality between socioeconomic groups have been attributed to differences in health behaviours such as smoking, lack of exercise, and poor diet[167-169], but SES is reported to be associated with mortality even when adjusting for these risk factors[170,171]. Sweden has a long history of economic equality, but over the last decades inequalities have increased faster than in other comparable countries[172]. However, Sweden still remains one of the world's most economically equal countries. Since all Swedish citizens have access to a universal public healthcare system with minimal cost to the patient, direct economic barriers such as not being able to afford specialist care and medications are unlikely.

SES affects mortality in most forms of cancer[173], and lower SES has been reported to be associated with poorer outcomes in Chronic Myeloid Leukaemia[174], AML[175], Myeloma[176], Lymphoma[177,178], as well as after HSCT[179]. Lower SES is associated with less chemotherapy and HSCT utilisation for both Acute Lymphoblastic Leukaemia and AML[180]. In a Swedish cohort of AML and myeloma, the differences in survival in different groups based on SES were reported to have increased from the 1970's to 2000's[176].

For MDS, data on the effect of SES on survival and disease characteristics is limited. In 2009, *Wang et al*. published a study using SEER data to evaluate the effect of neighbourhood SES on the survival of elderly MDS-patients[181]. They found that MDS patients with lower neighbourhood SES had a shorter survival, even after adjusting for comorbidity and other patient characteristics, and this effect was more pronounced among patients with low-risk disease. Studies from Canada[182] and the UK[183] failed to show any impact of SES on survival, but all of these included a limited number of patients. Furthermore,

similar to the study by *Wang et al.,* they did not use individual-level data, but rather based the SES on residential neighbourhood. A recent Danish study by *Bichel Lauritsen et al.* used a nationwide population-based approach with individual-level SES data to evaluate the effect on SES on clinical outcomes for MDS patients[184]. They found that MDS patients with a short education, compared to patients with a long education, had a poorer survival, were more likely to be transfusion dependent, and were more likely to be diagnosed with high-risk disease, and these patients had a markedly lower rate of HSCT. An American study reported that MDS patients with a longer education and a higher income were more likely to undergo a HSCT[185]. Data on the effect of SES on quality of care are scarce. One study shoved a minor association between household income and quality of care, as measured as the probability of assessment of iron levels before EPO-treatment, but not to the probability of baseline cytogenetic testing[186].

Aims of the thesis

By using a population-based approach, this thesis aims to expand the epidemiological knowledge of MDS and the related condition CMML. The thesis has a focus on prognostication, and the effect of comorbidity and other patient-related factors on outcome.

Paper I

Validate and compare prognostic scoring systems for MDS.

To present clinical characteristics including cytogenetics from a nationwide population-based cohort.

To study the effect of these clinical characteristics on survival and transformation to AML.

Paper II

Validate and compare prognostic scoring systems for CMML.

Validate and compare comorbidity indices in CMML.

To study the effect of comorbidity and other clinical characteristics on survival.

Paper III

To study whether socioeconomic indices, such as income and education, have an effect on survival in MDS.

To study whether these factors influence diagnostic procedures and treatment in MDS.

Paper IV

To present clinical characteristics including type of cytotoxic treatment and primary disease in therapy-related MDS.

To study whether type of cytotoxic treatment and primary disease affects survival in therapy-related MDS.

To study whether IPSS-R and the WHO 2016 classification are effective tools in prognostication of subgroups of therapy-related MDS.

To present data on previous malignancies in MDS patients, and compare these data with data from the general population.

Patients and methods

Data sources

Sweden has a population of 10.5 million. Nearly all specialised care and medications are publicly-funded with a low cost to the individual patient, and healthcare on equal conditions for the entire population is mandated by law. In Sweden, haematology is decentralised and most smaller hospitals have haematologists. The smaller hospitals are organised in greater regions with a university hospital in each of these greater regions. In general, there are one or several MDS-interested haematologists at each university hospital. All studies in this thesis are nationwide, thereby including virtually all individuals with MDS or CMML in Sweden diagnosed during the years under study. All cases were identified using the SMDSR. Individual-level record linkage between registers was made possible by use of the unique personal identity number assigned to all residents in Sweden at birth or upon permanent residency.

Papers I and II are retrospective populations-based cohort studies. In **paper I,** data from the SMDSR were used. This register is described in detail in the background section. During the 5-year study period (2009–2013) a total of 1345 patients diagnosed with MDS were reported to the SMDSR. No restriction in type of MDS or treatment was made. A total of 16 patients were excluded; 14 were considered to have AML or transforming to AML and two had died before the reported date of diagnosis. The final study population encompassed 1329 subjects. Information was obtained from the Swedish Adult Acute Leukemia Registry and the Swedish Cause of Death register to calculate transformation to AML.

In **paper II** the main data source was a detailed retrospective chart review. The study included 359 patients with CMML, representing all CMML cases diagnosed between 2009 and 2015 and reported to the SMDSR. Of these, 22 patients were excluded; 15 patients were considered to have primary AML, five did not fulfil the criteria for CMML, and two were diagnosed before 2009. In addition to data from the chart review, information was obtained from the Swedish Adult Acute Leukemia Registry to calculate transformation to AML.

Paper III and **paper IV** are population-based matched cohort studies using national health registers in combination with the SMDSR as data sources.
For the purpose of these and other studies, a dataset (MDSbase) was generated based on individual-level record linkages between the SMDSR and several

registers with national coverage at the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden (SCB) including:

1. The Swedish National Patient Register (NPR). The NPR includes hospital discharge diagnoses according to the ICD and covers all Swedish in-patient care from 1987 and onwards. Since 2001, diagnoses from specialised out-patient care (not including primary care) are also recorded[187].
2. The Swedish Cancer Register (SCR). The SCR was founded in 1958, and it is compulsory for both pathologists and clinicians to report all newly detected malignant diseases to the register. The SCR contains detailed information coded according to the Systematised Nomenclature of Medical–Clinical Terms (SNOMED) and International Classification of Diseases (ICD). All registered cancers are classified according to ICD-7, as well as the ICD version (ICD-9 from 1987, and ICD-10 from 1993) that was used during the time of diagnosis. Since 2005, the ICD for Oncology (ICD-O/3) is used. The register is reported to be of high quality and has high completeness[188].
3. The Swedish Prescribed Drug Register was established in 2005 and includes all dispensed prescribed drugs in the Swedish population, however no information on medications given at hospitals is available from this register[189].
4. The Swedish Cause of Death register (CDR). Some sort of central record regarding causes of death have been recorded since 1749 in Sweden. This is now organised in the CDR, a virtually complete register of all deaths in Sweden since 1952[190]. When a person dies, the responsible physician is required to complete a mandatory cause of death certificate (including the main and contributing causes of death, as well as any other significant diseases). At the CDR, a single cause of death is selected as the principal underlying cause of death, according to international coding guidelines developed by the WHO.
5. Integrated database for labour market research (LISA)[191]. The LISA database is a compilation of data from several registers at SCB and other authorities, it contains information on educational background, income, sick leave, and several other socioeconomic indicators for all Swedish citizens 16 years of age and older from 1990 onwards.
6. The Population Register (PR) is administered by SCB. The PR includes all persons registered in Sweden. Survival data for all studies was obtained from this register via the SMDSR.

Since participation in all government-administered registers is compulsory for all persons living in Sweden there is no selection bias from the aforementioned registers.

In **paper III**, the cohort consisted of all patients in the SMDSR with MDS, diagnosed between January 2009 and December 2018. Two patients had no registered income or education and were excluded. In all, the cohort included 2945 patients. The dataset also included 14,724 matched controls from the PR. Follow-up data was used to assess treatment with HMA and HSCT. In addition to the SMDSR, data from the NPR was used to find additional patients who had undergone HSCT. The NPR was also used to calculate CCI, estimating comorbidity.

In **paper IV** the cohort consisted of all patients with MDS in the SMDSR diagnosed 2009-2017. A total of 2705 patients were included, 423 (16%) of whom were classified as having t-MDS. The dataset also included 13,509 matched controls from the PR. For patients with t-MDS data on primary disease were obtained from the SCR and PR. As in paper III, comorbidity was estimated using CCI, including diagnoses for the NPR 10 years preceding MDS diagnosis. Causes of death were obtained from the CDR.

Methods

Data on cytogenetics for the period under study in **paper I** were incomplete in the SMDSR. Therefore, the full cytogenetics report was retrospectively retrieved from all the six clinical genetics laboratories that perform karyotype analyses in Sweden. The karyotype report and IPSS and IPSS-R cytogenetic scores were centrally reviewed by a clinical geneticist. This cytogenetic data were then uploaded to the SMDSR and used in the subsequent studies. In order to calculate transformation to AML, information was obtained from the Swedish Adult Acute Leukemia Registry and the Swedish Cause of Death Register.

For **paper II,** all 53 hospitals that had reported CMML patients to the SMDSR were contacted, and consent from each head of department was obtained for a chart review. The chart review was mainly done on site with access to the electronic medical records. In some cases, printed-out copies of the chart were used. Through the chart review, laboratory parameters at diagnosis, prior history of chemotherapy and radiation, comorbidities, transfusions, diagnostic procedures including cytogenetics and bone marrow morphology, and treatments were collected. Data was entered in a case report form and subsequently into a database. As in paper I, the karyotype report was reviewed centrally by a clinical geneticist. Comorbidities were defined the same way as they were in each of the original publications of CCI, HCT-CI, and MDS-CI.

For **papers III and IV**, the database MDSbase was used. Controls from the PR were randomly selected and matched 1:5 on age, sex, and county of residence.

MDSbase contains a total of 40,236 individuals (cases and controls), many hundreds of variables, and several millions of observations. In both studies CCI was used to assess comorbidity, and diagnoses from the NPR 10 years preceding MDS diagnosis were included. In **paper III,** an adjusted version of CCI for register data was used[192]. In **paper IV,** a recently-published version of CCI for Swedish register-based research was used[193]. Since t-MDS was the focus in **paper IV**, malignancies were excluded in the calculations of CCI to be able to compare t-MDS with de novo MDS.

Regarding SES in **paper III**, personal and household income was divided into quintiles. Data on education were collapsed from the original classification into three categories; ≤9 years, 10–12 years and ≥13 years of education.

Regarding the primary disease in **paper IV** the SCR was used for patients with a malignant primary disease and the NPR was used for non-malignant primary diseases. To define the primary disease in cases where there were multiple possible primary diseases all data in MDSbase were considered and the most likely primary disease was selected based on treatment traditions, time span between the primary disease and the diagnosis of MDS, and in some cases prescriptions from the Prescribed Drug Register.

Statistical analyses

In all studies, basic descriptive techniques were used to assess patient characteristics and describe the cohorts. *P*-values less than 0.05 were considered to indicate statistical significance. Overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Relative mortality was analysed with Cox proportional hazards models, yielding hazard ratios (HRs) with 95% confidence intervals (CIs).

In **paper I,** the effect of additional clinical parameters besides IPSS-R on survival was evaluated by constructing a Cox regression model including IPSS-R scores, the separate impacts of age, sex, bone marrow fibrosis, lactate dehydrogenase (LDH) and t-MDS. The proportional hazards assumption was formally tested for each model using Schoenfeld residuals[194].

In **paper II,** a Cox regression model was constructed to explore the independent effect of the comorbidity indices on survival. Comorbidity index scores were analysed as a continuous variable. Significant variables from the univariate analyses were considered in the multivariable analyses. The final variables were chosen using backward elimination and included age, monocyte count, CPSS-group, and CCI-score. To evaluate the Cox model, the Akaike information criterion (AIC) was calculated, and including the CCI score improved the AIC. The risk of transformation to AML was calculated

using the cumulative incidence function to account for the competing risk of death.

To evaluate the prognostic scoring systems in **papers I and II** and the comorbidity indices in **paper II** the Harrell concordance (C) index was used[195]. The C-index ranges between 0.5 and 1, where 1 stands for perfect discrimination and 0.5 for no discrimination at all. Indices were internally validated by bootstrapping, using 1000 samples. When comparing C-indices, the approach described by *Kang et al* was used[196]. In **papers I and II** all analyses were performed using R version 3.2.2 and 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics for Windows, Version 24 (IBM, Armonk, NY, USA).

In **paper III** potential interactions (such as differences in associations between cases and population comparator subjects) were analysed by stratified analyses and formally tested by adding interaction terms to the proportional hazards model. The probabilities of obtaining cytogenetic diagnostics, receiving HMA treatment or undergoing HSCT were assessed by Poisson regression using PROC GENMOD in SAS. All analyses in paper III were performed with SAS University Edition statistical software (SAS Inc).

In **paper IV** unadjusted logistic regression models were fitted to compare the likelihood of previous malignant disease between MDS patients and their matched controls, yielding odds ratios (ORs) and 95% CIs. To assess if type of cytotoxic treatment and type of primary disease were independently associated with OS a Cox regression model including age, type of previous cytotoxic treatment, type of primary disease, CCI, and IPSS-R was constructed. All analyses were performed using Stata 16 (StataCorp, TX, USA) and SPSS Statistics for Windows, Version 28 (IBM, NY, USA).

Ethical considerations

The studies in this thesis were approved by the ethics committee of Uppsala University (2014/176), with an amendment for the chart review of paper II (2014/176/1). Informed consent was not deemed necessary by the ethics committee. Many of the participants were diseased at the initiation of the studies and contacting their families for consent entails a risk of negative psychological impact on them. Asking for consent will also introduce selection bias in the studies, risking the population-based approach. The chart review in paper II can be considered a breach of personal integrity. This was limited by reducing the number of researchers involved in the data collection phase and by pseudo-anonymising the data during the data analysis. Paper II, as all studies in this thesis only contains aggregated data and no single individual can be identified from the papers. For inclusion in the SMDSR there is no need for written informed consent, but the patients should be informed that information is gathered in the register. For MDSbase, record linkages were performed at SCB and the National Board of Health and Welfare. The researchers had no access to the identity of the participants since all data in MDSbase were pseudo-anonymised at the National Board of Health and Welfare where the code-key is kept for a limited amount of time. The negative effects on the personal integrity of the study participants in the papers of this thesis are in all considered small, and by far outweighed by the scientific value of these studies.

Results and discussion

Paper I

Main findings and conclusions

The yearly crude incidence of MDS in Sweden was 2.9 per 100,000 inhabitants. The median OS was 27.8 months. For 973 patients (73% of the total population) there was complete data to calculate the IPSS and IPSS-R, and for 854 (64%) we could calculate the WPSS. Missing data was attributed to the lack of karyotyping in 334 patients (25%). Most separate components of the scoring systems showed good prognostic discrimination for both OS and progression to AML. The distribution of risk groups in WPSS, IPSS and IPSS-R is shown in table 2. More patients were placed in the higher-risk groups of WPSS compared to IPSS-R, 45% and 33% of the patients, respectively. Patients with t-MDS were more often in the higher-risk groups; 54% were in the IPSS-R high- or very high-risk group compared to 29% of patients with de novo MDS. When comparing our cohort with the original cohort of IPSS-R ours had older patients and more patients in the high risk categories.

One of the main aims of the study was to compare WPSS, IPSS, and IPSS-R using C-index, and we found that IPSS-R had better prognostic power for OS than IPSS and a trend towards better prognostic power than WPSS, (table 2). For patients younger than 70 years IPSS-R had significantly higher C-index of 0.76 as compared to both WPSS and IPSS with a C-index of 0.73. For this younger group where HSCT might be considered, correct prognostication is of particular importance. The effectiveness of the prognostic scoring systems was comparable for de novo-MDS and t-MDS.

Table 2: Risk score classification, survival in months and discriminative power between the scoring systems.

	Overall survival							
						p-value		
	n	**Median**	**HR**	**95% CI**	**C-index**	**vs WPSS**	**vs IPSS**	**vs IPSS-R**
WPSS					0.73		0.07	0.05
Very low risk	109	NR	0.49	(0.30-0.79)				
Low risk	207	65.6	1.00	(ref.)				
Intermediate risk	158	36.0	1.84	(1.35-2.50)				
High risk	247	19.9	3.20	(2.44-4.20)				
Very high risk	133	9.8	6.61	(4.90-8.92)				
IPSS					0.71	0.07		<0.001
Low risk	301	67.2	1.00	(ref.)				
Interm. risk I	370	31.1	2.91	(2.25-3.77)				
Interm. risk II	223	13.4	6.38	(4.88-8.34)				
High risk	79	10.8	10.22	(7.34-14.25)				
IPSS-R					0.74	0.05	<0.001	
Very low risk	130	NR	0.58	(0.39-0.87)				
Low risk	330	57.7	1.00	(ref.)				
Intermediate risk	196	29.8	2.14	(1.66-2.75)				
High risk	153	17.0	3.96	(3.08-5.10)				
Very high risk	164	9.3	7.23	(5.65-9.25)				

NR = Not reached, HR = Hazard ratio, CI = Confidence interval, WPSS = World health organisation classification-based scoring system, IPSS = International Prognostic Scoring System, IPSS-R = Revised International Prognostic Scoring System

The prognostic effect of additional clinical parameters was analysed (Figure 8). In addition to IPSS-R; higher age, male gender, elevated LDH and t-MDS independently reduced OS.

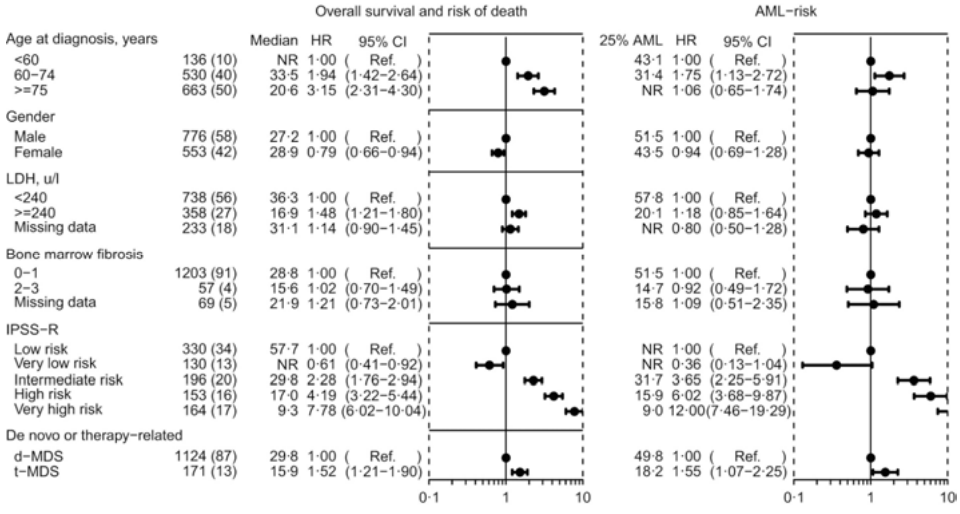

Figure 8. Multivariable analyses of additional characteristics and IPSS-R risk group, OS and AML-risk. AML = acute myeloid leukaemia, 25% AML = time (months) when 25% of patients had developed AML, CI = confidence interval, d-MDS = de novo MDS

In summary, in a dataset based on a nationwide population-based register, WPSS, IPSS and IPSS-R all represent valid and useful tools in predicting OS and progression to AML in MDS and in the subgroup of t-MDS. IPSS-R was the best prognostic tool.

Limitations

A general limitation throughout this thesis is the lack of mutational data. As all studies are based on existing data from retrospective sources, no data on mutations was available, which is a limitation since mutations have a well-known independent effect on prognosis.

Since paper I is based on data from SMDSR the quality of the study is highly dependent on the quality of the register. A limitation is that the quality of the data in SMDSR has not yet been validated in a formal study. Misclassification bias might occur, as the reporting clinicians might not have followed the instructions in the SMDSR, but in general this misclassification should be non-differential. There were also missing data, particularly for karyotype. Missing data was reduced by actively collecting the cytogenetic reports. However, these missing data were not random, as patients without a karyotype were older and had a shorter survival time. In the vast majority, the missing

karyotype data was due to the fact that a cytogenetic examination was never performed in the diagnostic work-up and thus reflects the clinical reality. The SMDSR has a high completeness compared to the SCR, but as discussed earlier underreporting of MDS might be a problem. How substantial this problem is in Sweden has not been studied. From the period under study the SMDSR includes no information on comorbidity or performance status, which are factors known to affect prognosis.

Paper II

Main findings and conclusions

This study included nationwide data from a large cohort of 337 patients with CMML. The median OS was 21.3 months. Most patients had a high WBC (MP-CMML; 63%) and low blasts (CMML-0; 55%). A history of cytotoxic treatment was reported in 24 patients, and these patients were considered to have t-CMML. Karyotyping was performed at diagnosis in 242 patients (72%). As expected, most patients had a normal karyotype, and only 75 (31%) had cytogenetic aberrations. Among those with an available karyotype, 14% were in the high-risk group according to the Spanish cytogenetic score, and trisomy 8 was the most common aberration.

The median survival of patients diagnosed at university hospitals was 23.0 months and at non-university hospitals 19.5 months. In table 3 we present the distribution and survival according to risk group for the prognostic scoring systems. The 96 patients for which we could not calculate the CPSS were older with a median age of 83 years, and had a median survival of 14.9 months, shorter than for the entire cohort. Kaplan–Meier curves for OS are presented in Figure 9.

Table 3: Risk score classification, survival in months, hazard ratios and discriminative power of the scoring systems.

		Overall survival			
All patients	**n**	**Median**	**HR**	**95% CI**	**C-index**
IPPS-R					0.60
Very low risk	46	25.3	1.00	ref.	
Low risk	95	30.8	1.03	0.68–1.56	
Intermediate risk	56	23.9	1.35	0.86–2.12	
High risk	38	12.4	1.80	1.10–2.93	
Very high risk	6	11.1	3.73	1.43–9.73	

CPSS					0.69
Low	46	52.2	1.00	ref.	
Intermediate 1	94	26.3	1.76	1.12–2.75	
Intermediate 2	86	18.7	3.11	1.99–4.87	
High	15	10.4	4.62	2.32–9.22	
MDAPS					0.65
Low	164	29.7	1.00	ref.	
Intermediate 1	91	21.3	1.42	1.06–1.91	
Intermediate 2	55	12.4	2.51	1.79–3.53	
High	18	10.4	3.43	2.01–5.85	
Mayo					0.66
Low	98	31.5	1.00	ref.	
Intermediate	122	25.4	1.42	1.04–1.94	
High	115	12.4	2.60	1.89–3.56	

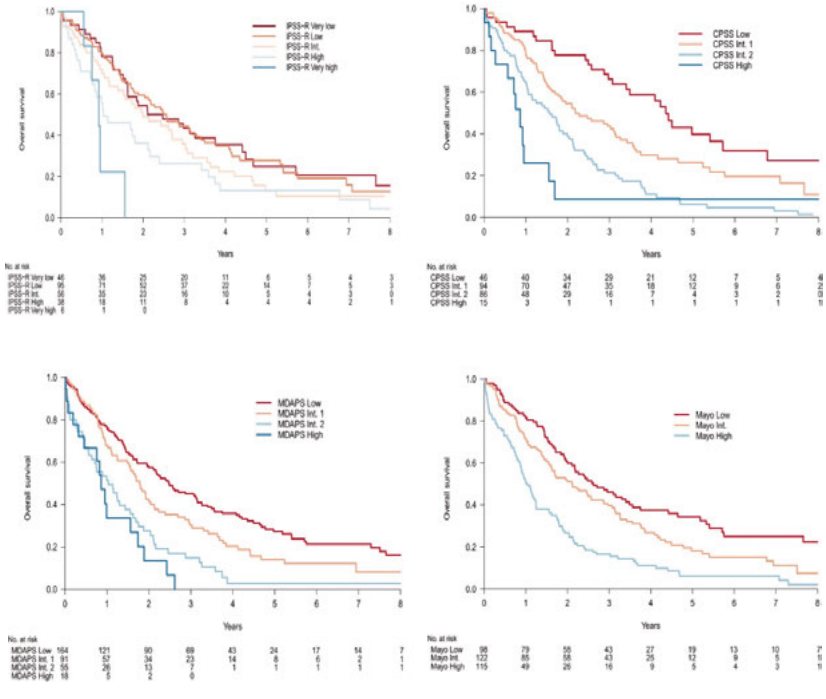

Figure 9. Overall survival categorised according to risk group in the prognostic scoring systems; IPSS-R, CPSS, MDAPS, and Mayo score.

To compare the prognostic scoring systems, C-index was used (table 3). Only the difference between CPSS and IPSS-R was significant ($P = 0.004$). Since only MD-CMML was included the original IPSS-R cohort, IPSS-R was also tested in this subgroup, but the prognostic power was similar. In a subgroup analysis of younger patients (aged <70 years) the C-index of CPSS was 0.78, significantly higher than the other scores. As with IPSS-R for MDS in **paper I,** this finding is worth highlighting; as accurate risk scoring is particularly important in this age group, where HSCT may be considered. We conclude that CPSS is the most powerful prognostic scoring system of the ones studied, and that IPSS-R should not be used in CMML.

As an association between CMML and autoimmune conditions has previously been reported from smaller or more restricted cohorts, we were interested in these comorbidities[146,147,197]. The overall prevalence of autoimmune conditions was 25%. Polymyalgia rheumatica was found in 8%, Hashimoto's thyroiditis in 7%, and psoriasis/psoriatic arthritis in 5% of patients. The association with autoimmune conditions raises several interesting research questions. Previous autoimmune conditions and their relation to possible common risk factors and their effect on prognosis merit further study. As discussed in the background, chronic inflammation from autoimmune disease may be involved in the pathogenesis of CMML. Moreover, chronic inflammation from autoimmune disease might act as a link between cardiovascular disease and CMML — in fact, cardiac disease was a common comorbidity in our present study, and ischaemic heart disease was the most frequent condition, found in 17% of patients.

This study represents the first validation and comparison of comorbidity indices in CMML. The C-indices for the CCI, HCT-CI and MDS-CI were 0.62, 0.61 and 0.59, respectively; these differences were non-significant. In a subgroup analysis of lower-risk CMML, the C-index of the CCI and HCT-CI improved; in this group the CCI was significantly better than the MDS-CI ($P = 0.03$). It seems like comorbidity has an impact on survival in lower-risk disease, whereas the poor prognosis of high-risk CMML makes the additional effect of comorbidity less important. Of the three tested comorbidity indices, CCI had the highest C-index and was the only comorbidity index significantly associated with survival in multivariable analyses including CPSS risk group, monocyte count, and age. One reason why the CCI was superior to the MDS-CI could be that it includes more comorbidities. However, the simplicity of the MDS-CI can be an advantage in clinical practice.

In conclusion, paper II presents data from a large nationwide cohort of patients with CMML. Comorbidity is prevalent, including a strikingly high prevalence of autoimmune conditions. Furthermore, comorbidity adds prognostic information in patients with lower-risk CMML, and the CCI gives more prognostic information than the HCT-CI and MDS-CI. Of the tested prognostic scoring systems, the CPSS appears to have a slightly better prognostic capacity than the MDAPS and Mayo score. IPSS-R should not be used in CMML.

Limitations

Data in paper II were based on a chart review. This increases the validity of data on disease characteristics and treatments as compared to paper I. In regard to comorbidity, the completeness of the data is highly dependent on a complete medical history being recorded in the charts. Since patients from all over Sweden were included, data were accessed from different systems for electronic medical records in different hospitals and regions. These systems gave access to varying parts of the patients' medical history, for most patients a complete medical history was obtained, but for some the access to, for example records from primary care was restricted. This might lead to an underestimation of the burden of comorbidity. Moreover, strict adherence to the definitions of different comorbidities in the comorbidity indices was not always possible. These definitions were sometimes based on outdated diagnostics or clinical findings. This introduces a somewhat subjective assessment by the researchers collecting the data, there is also a possibility that these assessments differ slightly between data collectors.

Paper III

Main findings and conclusions

In paper III, 2945 patients with MDS diagnosed 2009–2018 were analysed in regard to the effect of SES on survival, diagnostic procedures, and treatment. Both income and education were correlated to OS. When adjusting for prognostic factors (age, sex, WHO subgroup, comorbidity, transfusion dependency, and IPSS-R) the mortality was 50% higher in patients with the lowest income compared to the highest income (HR 1.5 95% CI 1.3–1.8) and 40% higher among patients with the shortest education compared to the longest (HR 1.4, 95% CI 1.2–1.6). As SES is known to affect survival in the general population, controls were analysed, and a similar association was found. This well-known fact that survival in the general population is associated with SES does not explain the finding in MDS patients. Since MDS has a relatively short survival, the background survival will have a limited effect on survival for MDS patients.

Regarding treatment, the probability of receiving HMA treatment was 40% lower for patients with the lowest income compared to the highest income (RR 0.6, 95% CI 0.5–0.8) and 20% lower among patients with the shortest education as compared to those with the longest (RR 0.8, 95% CI 0.7–1.0)

Among the 1371 patients younger than 75 years at diagnosis, 242 patients (18%) underwent HSCT. In adjusted analyses income (RR 0.3, 95% CI 0.2–0.5) was strongly associated with the probability of undergoing HSCT. Having a cytogenetic evaluation at diagnosis was used as a measurement of the quality of the diagnostic work-up, and patients with lower incomes had a

higher probability of not undergoing cytogenetic diagnostics (RR lowest compared to highest income 2.1 95% CI 1.5–2.9).

The finding that lower SES was associated with poorer survival, a less thorough diagnostic work-up, and a less effective treatment needs to be further studied regarding the underlying mechanisms behind these inequalities. More research is needed to explore which exact risk factors influence the survival differences, and how healthcare providers can mitigate these inequalities. Raising awareness of health inequality and increasing adherence to guidelines, including recently published national guidelines, can hopefully decrease this inequality. Information on health-related issues needs to be appropriately designed so that people with a low level of education can understand it and communication by healthcare professionals must be appropriately tailored to the level of education and health literacy of the individual patient.

Limitations

Data on treatment with HMAs were only collected from the follow-up data in the SMDSR. The reliability of treatment data in SMDSR has not yet been evaluated. Since the development of MDS is insidious, the time-point when the diagnosis is made will have an impact on survival. Some patients will get their diagnosis at an early stage and some at a later stage, and in the latter case, a shorter life span stems from later diagnosis rather than earlier death. The time-point at which a patient is diagnosed is not random and it might be influenced by socioeconomic factors. Richer and more educated persons might seek medical attention earlier if symptoms develop, or more often be subjected to regular check-ups. This introduces lead time bias, for which there was no way to fully control. There are indications of lead time bias in the study, as a lower percentage of high-income patients presented with erythrocyte transfusion dependency. However, adjustments for transfusion dependency and IPSS/IPSS-R risk class should control this; at least in part. The difference in cytogenetic evaluation cannot be explained by lead time bias, as patients with a more severe disease at diagnosis should be more likely to go through a full diagnostic work-up.

Comorbidities are affected by SES, and we used CCI to adjust for this. However, CCI is just an index and cannot fully account for comorbidity. Other health-related factors such as nutritional status, obesity, physical activity, smoking, alcohol, and drug use could also influence survival and treatment decisions. These factors might also be associated with SES and could confound our results. Unfortunately, these factors were not measurable in this retrospective register-based approach.

Paper IV

Main findings and conclusions

In this first-ever nationwide study on t-MDS based on 2705 MDS patients diagnosed between 2009 and 2017, including 423 (16%) with t-MDS, we combined the SMDSR with several other national health registers. Patients with t-MDS had a shorter median survival as compared to de novo MDS (15.8 months vs 31.1 months, $p < 0.001$). Higher proportions of t-MDS patients were found in the high (24%) and very high (26%) IPSS-R groups compared to de novo MDS (15% and 14%, respectively) ($p < 0.001$). A major contributing factor was the large number of t-MDS patients with high-risk cytogenetics (39% with poor or very poor cytogenetic risk groups).

Treatment with either chemotherapy alone or chemotherapy and radiation in combination for the primary disease was associated with significantly shorter survival (13.3 and 9.0 months, respectively) than treatment with radiation only (34.8 months) ($p < 0.001$) (Figure 10a). Having a non-malignant disease or a solid tumour as a primary disease was associated with a longer OS, (26.1 and 22.3 months, respectively) compared with those with a haematological malignancy (9.0 months) ($p < 0.001$) (Figure 10b). One reason for this poor survival might be death from the primary disease, as patients with a previous haematological malignancy had their primary malignancy more often stated as their cause of death (45%) than patients with a previous solid tumour (15%). As MDS patients with a previous hematological malignancy seems to constitute a separate group with a dismal prognosis, additional research into the underlying mechanisms and potential treatments for this group is warranted.

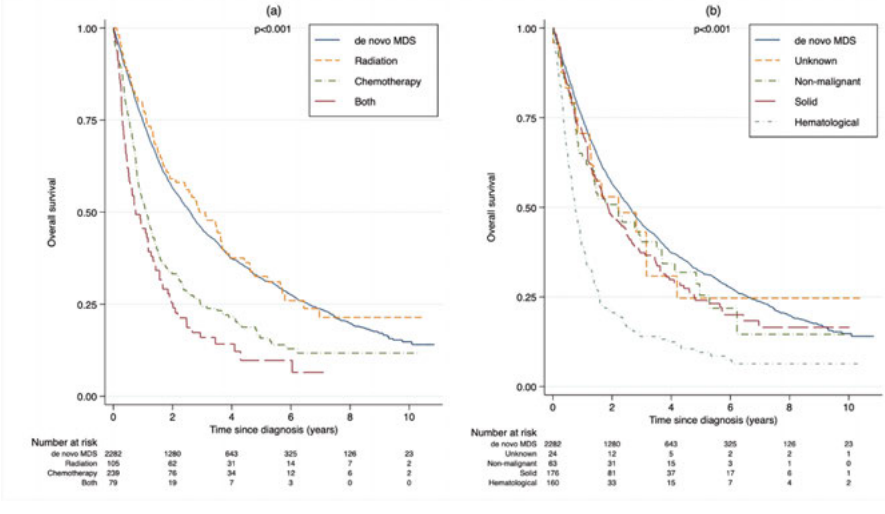

Figure 10: OS of de novo MDS and subgroups of t-MDS.
a. OS by type of cytotoxic treatment. b. OS by type of primary disease

One of the aims of the study was to validate IPSS-R and the WHO classification in t-MDS. IPSS-R effectively discriminated between different risk groups in t-MDS overall, as well as in subgroup-analyses based on type of cytotoxic treatment. Furthermore, IPSS-R could separate risk groups for patients with solid tumours and non-malignant disease, but to a lesser extent for patients with haematological malignancy as their primary disease.

The different disease entities in the WHO classification were combined according to their median survival into three groups (good, intermediate, and poor). There was a difference in t-MDS survival according to the WHO-based risk groups; both good versus intermediate ($p < 0.002$); and intermediate versus poor ($p < 0.001$). In subgroups based on type of cytotoxic treatment, the WHO classification could also discriminate between different risk groups. The classification was also effective in patients with a previous solid tumour, but was less effective for patients with previous haematological malignancies.

To assess whether the type of cytotoxic treatment and type of primary disease were independently associated with OS, a multivariable analysis was constructed. As shown in Figure 11, age group, type of previous cytotoxic treatment, type of primary disease, CCI, and risk group according to IPSS-R were independently associated with survival.

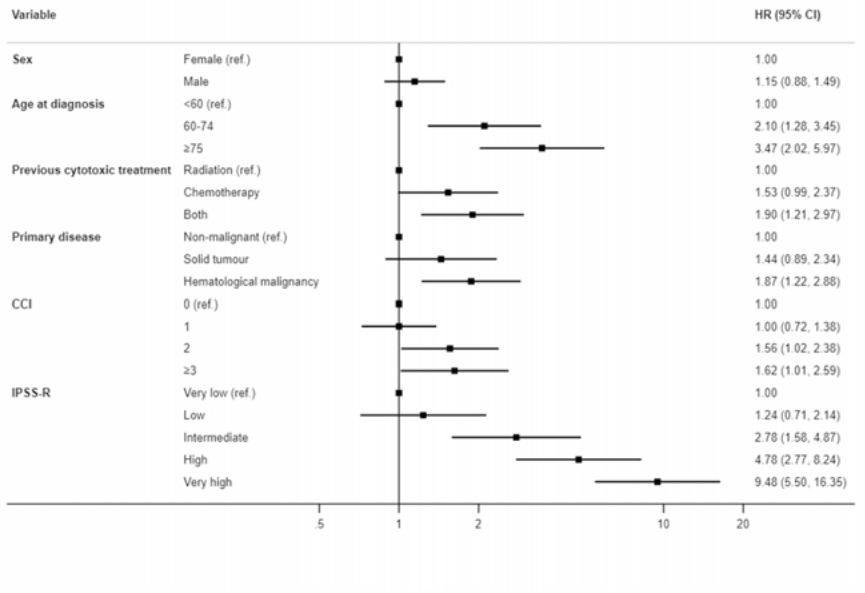

Figure 11: Multivariable analysis of the OS of t-MDS patients by patient and disease characteristics.

Regarding the prior history of cancer among cases and controls, MDS patients were more likely to have had a solid tumour than controls (OR = 1.34, 95% CI: 1.21–1.49) and for prior haematological malignancies there was a strikingly high six-fold increase in MDS patients (OR = 6.09, 95% CI: 4.87–7.61). The long latency between the primary disease and MDS diagnosis suggests that they represent separate previous conditions and not misclassification. Shared pathophysiological mechanisms and risk factors such as clonal haematopoiesis and intensive treatments with high doses of chemotherapy, represent possible causes for this strong association.

The most important finding of this study is that t-MDS patients with previous cytotoxic treatment in the form of radiation only, have clinical characteristics and prognoses comparable to patients with de novo MDS. They have transfusion dependency, blast counts, and cytogenetic risk profiles with a striking resemblance to de novo MDS, in sharp contrast to patients treated with chemotherapy or a combination of chemotherapy and radiation who have a significantly higher risk profile. Patients previously treated with radiation should be viewed as de novo-MDS with regard to prognostication and treatment. Standard risk stratification and morphologic classification is meaningful in t-MDS, and it should be classified the same way de novo MDS is classified but with recognition that type of prior disease and cytotoxic treatment affects the prognosis.

Limitations

The main limitation of this study is the limited information on the treatment for the primary disease. We did not have information on either doses or field of radiation, or on type of chemotherapy. More detailed information on treatment would have made it possible to draw conclusions regarding specific cytotoxic agents and radiation doses. In cases with multiple possible primary diseases, information on treatments would have made the definition of the primary disease more precise.

Mutational data would have allowed assessment of the mutational spectrum in different subgroups of t-MDS, and could possibly further clarify the reason for the poor prognosis in certain subgroups. Further, mutational data would have made validation of the IPSS-M possible, and could have made it possible to study the effect on germline predisposition.

The finding that a prior haematological malignancy was six times more frequent in MDS patients than controls might be influenced by diagnostic suspicion bias and detection bias. Patients with haematological malignancies will be followed by haematologists who might more readily suspect MDS, and these patients might be subjected to regular bone marrow examinations, making diagnosis of MDS more probable.

Concluding remarks and further perspectives

In this thesis, a population-based approach has expanded the epidemiological knowledge of MDS and the related condition CMML. All four papers in this thesis are unique in that they provide first-ever nationwide data. In contrast to clinical trials and more restricted cohorts, nationwide data is highly generalisable and findings will apply to MDS patients in general.

Prognostication with IPSS-R in MDS, and CPSS in CMML, was effective in our real-world data. Comorbidity is common in CMML, and assessing it with CCI gives prognostic information. Autoimmune conditions are highly prevalent in CMML. Socioeconomic factors such as income and education are associated with survival in MDS. Patients with a lower SES have shorter survival, undergo a less thorough diagnostic work-up, and are less likely to receive effective treatment with hypomethylating agents and HSCT. Therapy-related MDS has a poor prognosis, but this group is heterogeneous, and prognostication and classification intended for de novo MDS is effective in t-MDS. Type of prior disease and cytotoxic treatment have substantial effects on prognosis. The subgroup treated with only radiation for their primary disease is similar to patients with de novo MDS, and should be regarded as having de novo MDS with regards to prognostication and treatment.

For this thesis, nationwide registers with high quality data have been a valuable research tool. An extensive amount of high-quality research using these registers has been published in Sweden but the enormous amount of data is still somewhat of a hidden gem for scientists. Automated data entry directly from the electronic charts has the possibility to take these registers to the next level. It would reduce the workload on reporting clinicians and increase the number of variables and follow-ups that are possible to include. Directly-uploaded molecular and treatment data would increase the registers' usefulness in clinical work and as well as a research tool. Dynamic prognostic assessments and follow-up on treatments might also be included to aid clinicians in their decision making.

In further research regarding prognostication, disease specific characteristics should be combined with patient specific characteristics such as comorbidities and previous exposure to cytotoxic agents. Their interplay and effect on prognosis and response to treatment should be studied, and population-based data provides a solid ground for these future studies. For rare subgroups, such as MDS with a previous haematological malignancy or CMML with a

prior autoimmune condition, international collaboration, combining several population-based cohorts, can be one way forward.

Many unmet needs remain for MDS-patients, and hopefully the findings presented here have contributed to further research and development in MDS — a small step towards the long-term goal of prolonging survival and improving quality of life for patients with MDS.

Populärvetenskaplig sammanfattning på svenska

Myelodysplastiska syndrom (MDS) är en grupp blodcancersjukdomar som uppstår som en följd av genetiska fel i arvsmassan hos blodstamcellerna i benmärgen. Dessa förändringar leder till myelodysplasi, vilket innebär att benmärgen inte tillverkar normala blodceller utan istället onormala, dåligt utvecklade och dåligt fungerande blodceller. Vanliga symptom är trötthet pga. brist på röda blodkroppar, infektioner pga. brist på vita blodkroppar och blödningar pga. brist på blodplättar. MDS är relativt ovanligt, i Sverige diagnosticeras årligen ca 400 personer med MDS och förekomsten ökar med stigande ålder. Medelålder vid diagnos är omkring 75 år. Prognosen vid MDS är mycket varierande och vissa patienter kan leva många år medan andra bara lever några månader efter diagnos. I omkring 30 % av fallen övergår sjukdomen i akut myeloisk leukemi. Den enda botande behandlingen mot MDS är benmärgstransplantation men detta är främst aktuellt hos yngre patienter med högrisksjukdom.

Kronisk myelomonocytleukemi (KMML) har tidigare räknats som ett av de Myelodysplastiska syndromen men är nu en egen sjukdomsentitet. KMML är ovanligt och i Sverige insjuknar ca 50 personer varje år, sjukdomen har många likheter med MDS.

Syftet med denna avhandling är att med epidemiologiska metoder studera MDS och den närliggande sjukdomen KMML. Grunden för avhandlingen är det svenska MDS-registret. Detta register startades 2009 och innehåller nu ca 5000 patienter. Nästan alla som diagnosticeras med MDS eller KMML inkluderas i det svenska MDS-registret vilket gör att studierna och slutsatserna i denna avhandling i hög grad kan sägas vara generaliserbara och gälla MDS-patienter i allmänhet.

I studie I inkluderade vi samtliga 1329 patienter som diagnosticerats med MDS 2009–2013 och rapporterats till svenska MDS-registret. I studien validerade och jämförde vi tre olika prognostiska system (IPSS, IPSS-R och WPSS), som inkluderar resultat av blodprover och benmärgsprov för att kunna klassificera patienterna avseende prognos. I studien visade vi att IPSS-R hade den bästa förmågan att förutsäga överlevnad.

I studie II granskades journaler från alla 337 patienter med KMML inkluderade i svenska MDS-registret med diagnos 2009–2015. Studien syftade till

att jämföra de prognostiska systemen IPSS-R, CPSS, MDAPS och Mayo score och vi fann att CPSS hade något bättre förmåga att förutsäga överlevnad.

Eftersom de flesta patienter med KMML är äldre har de ofta andra sjukdomar dvs. samsjuklighet. Denna studie är den första som undersöker sjukdomsindex för samsjuklighet vid KMML. Vi ville undersöka om de tre sjukdomsindexen Charlson Comorbidity Index (CCI), Haematopoietic cell transplantation-specific Comorbidity Index (HCT-CI) och Myelodysplastic Syndrome-Specific Comorbidity Index (MDS-CI) kunde användas vid KMML och vilket som var bäst. Vi fann att samsjuklighet hade prognostisk betydelse främst hos de patienter som hade lågrisksjukdom och att CCI var något bättre än de övriga indexen. Vi visade också att autoimmuna sjukdomar var mycket vanligt, 25 % hade en sådan diagnos innan KMML-diagnosen.

Studie III omfattade 2945 patienter med MDS inkluderade i det svenska MDS-registret 2009–2018. I denna studie ville vi undersökta om socioekonomiska faktorer som utbildning och inkomst påverkade överlevnad och behandling vid MDS. Om man justerade för ålder, kön, MDS-riskgrupp och samsjuklighet var överlevnaden 50 % kortare hos dem med lägst inkomst jämfört med dem med högst inkomst. Överlevnaden var 40 % kortare hos dem med endast grundskoleutbildning jämfört med universitetsutbildning. I kontrollgruppen, som bestod av patienter utan MDS, fann vi liknande koppling mellan överlevnad och inkomst/utbildning. Personer med de högsta inkomsterna genomgick oftare benmärgstransplantation. Fullständig utredning med cytogenetik var också vanligare bland dem med högre inkomst.

Studie IV omfattade 2705 patienter med MDS inkluderade i det svenska MDS-registret 2009–2017. Fokus var på de 423 patienter (16 %) som hade terapirelaterad MDS (t-MDS) och denna studie var den första nationella studien på t-MDS som gjorts. Terapirelaterad innebär att patienterna tidigare behandlats med strålning eller cellgifter mot en cancer eller autoimmun sjukdom. MDS som inte är terapirelaterad kallas för de novo MDS. T-MDS karaktäriseras av sämre prognos och man har tidigare trott att patienter med t-MDS har varit en homogen grupp med kort överlevnad där prognostisering och klassificering som används för de novo MDS inte har någon roll.

I studien visar vi att prognostiska system och klassificering som används vid de novo MDS fungerar bra vid t-MDS. Vi visar vidare att de patienter som enbart behandlats med strålning för sin primärsjukdom är mycket lika patienter med de novo MDS. Vi menar därför att dessa patienter ska betraktas som de novo MDS och inte som t-MDS. Vi visar att MDS-patienter har en sex gånger ökad risk att ha haft en tidigare blodcancer jämfört med matchade kontroller, vidare har de en 34 % ökad risk att ha haft en tidigare solid cancer. De t-MDS patienter som haft en tidigare blodcancer innan sin MDS-diagnos hade en mycket dålig prognos, delvis pga. död i den tidigare blodcancersjukdomen.

Sammanfattningsvis bidrar denna avhandling med kunskap om MDS och KMML genom nationella populationsbaserade studier. Vi visar att prognos-

tiska system ger viktig information vid MDS, KMML och t-MDS. Vidare visar vi att sjukdomsindex kan användas vid KMML och att patienter med KMML ofta har autoimmuna sjukdomar. Vi visar också att socioekonomiska faktorer som utbildning och inkomst påverkar överlevnad och behandlingsbeslut vid MDS. Patienter med t-MDS som tidigare enbart behandlats med strålning kan betraktas som de novo MDS.

Ytterligare forskning baserat på svenska nationella register kommer förhoppningsvis fortsätta öka kunskapen om dessa fascinerade sjukdomar och i slutändan leda till ett bättre och längre liv hos patienter med MDS och KMML.

Acknowledgements

This thesis is the result of the hard work from a lot of people, thank you all!
A big heartfelt thank you to my main supervisor **Elisabeth Ejerblad**. Thanks for introducing me to this field and for letting me grow as a researcher. We did it together!

I also would like to express my most sincere thanks to:
Martin Jädersten, my co-supervisor, for your sharp analysing abilities, encouragement, and expert knowledge on everything from Cox regression to English punctuation.

Sören Lehmann, my other co-supervisor for your support and advice. Looking forward to further work together in the borderlands of MDS and AML.

MDS guru **Eva Hellström-Lindberg**, for paving the road for MDS research in Sweden. Thank you for excellent comments on manuscripts and strategical advice regarding publications.

Johanna Ungerstedt, your energy and constant optimism is inspiring. I learned a lot from the weeks in your lab with excellent support from **Matilda Kjellander**. Looking forward to future collaborations on CMML!

My sincere appreciation to all colleagues who have reported patients to the MDS register and to the data managers at respective RCC, by keeping the MDS register of high quality you made this thesis possible. Thanks to the members of the Swedish MDS-group and other co-authors: **Lars Nilsson, Hege Garelius, Bengt Ramussen, Petter Willner Hjelm, Mats Lambe, Johan Sundberg, Ellen Backlund** and **Marie Engvall.**

For the statistical support; **Folke Folkvaljon, Anders Berglund and Caroline Weibull** and at RCC Mellansverige, biostatistician **Marit Holmqvist**.

For financial support for this thesis: Insamlingstiftelsen Lions cancerforskningsfond Mellansverige Uppsala-Örebro. Naeslund stipendiefond, Norrlands nation and Olga Jönssons stipendiefond, Uppsala Universitet.

Thanks to my colleagues at the section of haematology in Uppsala, we have a truly inspiring workplace: **Martin Höglund, Kristina Carlsson, Helene Hallböök, Ulla Olsson Strömberg, Mattias Mattsson, Torbjörn Karlsson, Sara Rosengren, Anna Robelius, Tobias Tolf, Stina Söderlund, Karin Larsson, Emma Bergfelt Lennmyr, Hassan Othman Al Khmis, Albin Österroos, Sofia Vikman, and Klara Svedevall.** Previous and current head of department; **Honar Cherif and Gunnar Larfors** for good leadership and directing Uppsala-haematology forward. To all the staff at haematology ward 101A and our out-patient department at Akademiska sjukhuset - thank you all!

Tobias Sjöblom who got me interested in research in the first place and to **Ricard Olsson** who directed my interest to the field of haematology.

Henrik Benoni, Andreas Lundin, and Aindreas O'Neill from the iron/gym-gang in medical school, thanks for our travels, dinners and great conversations. My dear friend **Divan Ishak** for our regular lunches at the hospital and for inspiring discussions about everything and nothing. Long-time friend **Gustav Ståhl**, for always being there.

My mother **Anna-Lena, sister Anna, and all my family**, for your love and support.

Marijela, my love. I am so lucky to have you by my side. **Theo and Julia**, thank you for your unconditional love and affection, and for showing me what is important in life. Together we are the perfect team!

References

1. Thomas ML. The impact of myelodysplastic syndromes on quality of life: lessons learned from 70 voices. *J Support Oncol* 2012; **10**(1): 37-44.
2. Efficace F, Gaidano G, Breccia M, et al. Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes. *British journal of haematology* 2015; **168**(3): 361-70.
3. Stauder R, Yu G, Koinig KA, et al. Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study. *Leukemia* 2018; **32**(6): 1380-92.
4. Zeidan AM, Wang R, Davidoff AJ, et al. Disease-related costs of care and survival among Medicare-enrolled patients with myelodysplastic syndromes. *Cancer* 2016; **122**(10): 1598-607.
5. Zhao J, Dahlen T, Edgren G. Costs associated with transfusion therapy in patients with myelodysplastic syndromes in Sweden: a nationwide retrospective cohort study. *Vox Sang* 2021; **116**(5): 581-90.
6. Ejerblad E. Myelodysplastiskt syndrom (MDS) Rapport för diagnosår 2009-2021: Regionalt cancercentrum, Uppsala Örebro, 2022.
7. Cogle CR. Incidence and Burden of the Myelodysplastic Syndromes. *Current hematologic malignancy reports* 2015; **10**(3): 272-81.
8. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood* 2008; **112**(1): 45-52.
9. Roman E, Smith A, Appleton S, et al. Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004-15. *Cancer epidemiology* 2016; **42**: 186-98.
10. Radlund A, Thiede T, Hansen S, Carlsson M, Engquist L. Incidence of myelodysplastic syndromes in a Swedish population. *European journal of haematology* 1995; **54**(3): 153-6.
11. Kontro S, Raitanen J, Porkka K, Auvinen A. Incidence of myelodysplastic syndromes in Finland 1997-2016. *Leukemia research* 2022; **116**: 106839.
12. Zeidan AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: Why characterizing the beast is a prerequisite to taming it. *Blood reviews* 2019; **34**: 1-15.
13. Cogle CR, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. *Blood* 2011; **117**(26): 7121-5.
14. Buckstein R, Jang K, Friedlich J, et al. Estimating the prevalence of myelodysplastic syndromes in patients with unexplained cytopenias: a retrospective study of 322 bone marrows. *Leukemia research* 2009; **33**(10): 1313-8.

15. Neukirchen J, Schoonen WM, Strupp C, et al. Incidence and prevalence of myelodysplastic syndromes: data from the Dusseldorf MDS-registry. *Leukemia research* 2011; **35**(12): 1591-6.
16. Lauritsen TB, Norgaard JM, Dalton SO, Gronbaek K, El-Galaly TC, Ostgard LSG. 10-year nationwide trends in incidence, treatment patterns, and mortality of patients with myelodysplastic syndromes in Denmark. *Leukemia research* 2023; **128**: 107056.
17. Steensma DP. Does early diagnosis and treatment of myelodysplastic syndromes make a difference? *Best practice & research Clinical haematology* 2019; **32**(4): 101099.
18. Granfeldt Ostgard LS, Medeiros BC, Sengelov H, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(31): 3641-9.
19. Hulegardh E, Nilsson C, Lazarevic V, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. *American journal of hematology* 2015; **90**(3): 208-14.
20. Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. *Blood* 2013; **122**(25): 4021-34.
21. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *The New England journal of medicine* 2014; **371**(26): 2488-98.
22. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *The New England journal of medicine* 2014; **371**(26): 2477-87.
23. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 2013; **122**(22): 3616-27; quiz 99.
24. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. *Nature reviews Cancer* 2017; **17**(1): 5-19.
25. Ogawa S. Genetics of MDS. *Blood* 2019; **133**(10): 1049-59.
26. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia* 2014; **28**(2): 241-7.
27. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* 2011; **478**(7367): 64-9.
28. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med* 2020; **26**(10): 1549-56.
29. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood* 2007; **110**(13): 4385-95.
30. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(8): 820-9.

31. Sole F, Espinet B, Sanz GF, et al. Incidence, characterization and prognostic significance of chromosomal abnormalities in 640 patients with primary myelodysplastic syndromes. Grupo Cooperativo Espanol de Citogenetica Hematologica. *British journal of haematology* 2000; **108**(2): 346-56.
32. Behrens A, van Deursen JM, Rudolph KL, Schumacher B. Impact of genomic damage and ageing on stem cell function. *Nature cell biology* 2014; **16**(3): 201-7.
33. Rollison DE, Epling-Burnette PK, Park JY, et al. Telomere length in myelodysplastic syndromes. *Leukemia & lymphoma* 2011; **52**(8): 1528-36.
34. Colla S, Ong DS, Ogoti Y, et al. Telomere dysfunction drives aberrant hematopoietic differentiation and myelodysplastic syndrome. *Cancer cell* 2015; **27**(5): 644-57.
35. Kristinsson SY, Bjorkholm M, Hultcrantz M, Derolf AR, Landgren O, Goldin LR. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(21): 2897-903.
36. Anderson LA, Pfeiffer RM, Landgren O, Gadalla S, Berndt SI, Engels EA. Risks of myeloid malignancies in patients with autoimmune conditions. *British journal of cancer* 2009; **100**(5): 822-8.
37. Glenthoj A, Orskov AD, Hansen JW, Hadrup SR, O'Connell C, Gronbaek K. Immune Mechanisms in Myelodysplastic Syndrome. *International journal of molecular sciences* 2016; **17**(6).
38. Ganan-Gomez I, Wei Y, Starczynowski DT, et al. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. *Leukemia* 2015; **29**(7): 1458-69.
39. Raza A, Gezer S, Mundle S, et al. Apoptosis in bone marrow biopsy samples involving stromal and hematopoietic cells in 50 patients with myelodysplastic syndromes. *Blood* 1995; **86**(1): 268-76.
40. Trowbridge JJ, Starczynowski DT. Innate immune pathways and inflammation in hematopoietic aging, clonal hematopoiesis, and MDS. *J Exp Med* 2021; **218**(7).
41. Pronk E, Raaijmakers M. The mesenchymal niche in MDS. *Blood* 2019; **133**(10): 1031-8.
42. Bannon SA, DiNardo CD. Hereditary Predispositions to Myelodysplastic Syndrome. *International journal of molecular sciences* 2016; **17**(6).
43. Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. *Blood* 2017; **130**(4): 424-32.
44. Sakurai M, Kunimoto H, Watanabe N, et al. Impaired hematopoietic differentiation of RUNX1-mutated induced pluripotent stem cells derived from FPD/AML patients. *Leukemia* 2014; **28**(12): 2344-54.
45. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nature genetics* 2011; **43**(10): 1012-7.
46. Polprasert C, Schulze I, Sekeres MA, et al. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. *Cancer cell* 2015; **27**(5): 658-70.
47. Strom SS, Gu Y, Gruschkus SK, Pierce SA, Estey EH. Risk factors of myelodysplastic syndromes: a case-control study. *Leukemia* 2005; **19**(11): 1912-8.
48. Yarosh R, Roesler MA, Murray T, et al. Risk factors for de novo and therapy-related myelodysplastic syndromes (MDS). *Cancer causes & control : CCC* 2021; **32**(3): 241-50.

49. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. *Blood* 2003; **102**(1): 43-52.
50. Ganser A, Heuser M. Therapy-related myeloid neoplasms. *Current opinion in hematology* 2017; **24**(2): 152-8.
51. Heaney ML, Golde DW. Myelodysplasia. *The New England journal of medicine* 1999; **340**(21): 1649-60.
52. Sekeres MA, Taylor J. Diagnosis and Treatment of Myelodysplastic Syndromes: A Review. *Jama* 2022; **328**(9): 872-80.
53. Greenberg PL, Stone RM, Al-Kali A, et al. NCCN Guidelines(R) Insights: Myelodysplastic Syndromes, Version 3.2022. *Journal of the National Comprehensive Cancer Network : JNCCN* 2022; **20**(2): 106-17.
54. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; **127**(20): 2391-405.
55. Nimer SD. Clinical management of myelodysplastic syndromes with interstitial deletion of chromosome 5q. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(16): 2576-82.
56. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009; **114**(5): 937-51.
57. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood* 2020; **136**(2): 157-70.
58. Grob T, Al Hinai ASA, Sanders MA, et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood* 2022; **139**(15): 2347-54.
59. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. *Blood* 2022.
60. Layton DM, Mufti GJ. Myelodysplastic syndromes: their history, evolution and relation to acute myeloid leukaemia. *Blut* 1986; **53**(6): 423-36.
61. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *British journal of haematology* 1982; **51**(2): 189-99.
62. Jaffe ES. Pathology and genetics of tumours of haematopoietic and lymphoid tissues: Iarc; 2001.
63. Swerdlow SH. WHO classification of tumours of haematopoietic and lymphoid tissues. *WHO classification of tumours* 2008; **22008**: 439.
64. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* 2022; **36**(7): 1703-19.
65. Tanaka TN, Bejar R. MDS overlap disorders and diagnostic boundaries. *Blood* 2019; **133**(10): 1086-95.
66. Bono E, McLornan D, Travaglino E, et al. Clinical, histopathological and molecular characterization of hypoplastic myelodysplastic syndrome. *Leukemia* 2019; **33**(10): 2495-505.
67. Stahl M, DeVeaux M, de Witte T, et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. *Blood advances* 2018; **2**(14): 1765-72.

68. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* 2015; **126**(1): 9-16.
69. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. *Leukemia research* 2007; **31**(6): 727-36.
70. Valent P, Bain BJ, Bennett JM, et al. Idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of uncertain significance (IDUS), and their distinction from low risk MDS. *Leukemia research* 2012; **36**(1): 1-5.
71. Kwok B, Hall JM, Witte JS, et al. MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance. *Blood* 2015; **126**(21): 2355-61.
72. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood* 2017; **129**(25): 3371-8.
73. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997; **89**(6): 2079-88.
74. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007; **25**(23): 3503-10.
75. Bowen DT, Fenaux P, Hellstrom-Lindberg E, de Witte T. Time-dependent prognostic scoring system for myelodysplastic syndromes has significant limitations that may influence its reproducibility and practical application. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(7): 1180; author reply 1-2.
76. Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *Haematologica* 2011; **96**(10): 1433-40.
77. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012; **120**(12): 2454-65.
78. Pfeilstocker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. *Blood* 2016; **128**(7): 902-10.
79. Mishra A, Corrales-Yepez M, Ali NA, et al. Validation of the revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes. *American journal of hematology* 2013; **88**(7): 566-70.
80. Neukirchen J, Lauseker M, Blum S, et al. Validation of the revised international prognostic scoring system (IPSS-R) in patients with myelodysplastic syndrome: a multicenter study. *Leukemia research* 2014; **38**(1): 57-64.
81. Sekeres MA, Swern AS, Fenaux P, et al. Validation of the IPSS-R in lenalidomide-treated, lower-risk myelodysplastic syndrome patients with del(5q). *Blood cancer journal* 2014; **4**: e242.
82. Ok CY, Hasserjian RP, Fox PS, et al. Application of the international prognostic scoring system-revised in therapy-related myelodysplastic syndromes and oligoblastic acute myeloid leukemia. *Leukemia* 2014; **28**(1): 185-9.
83. Zeidan AM, Al Ali N, Barnard J, et al. Comparison of clinical outcomes and prognostic utility of risk stratification tools in patients with therapy-related vs de novo myelodysplastic syndromes: a report on behalf of the MDS Clinical Research Consortium. *Leukemia* 2017; **31**(6): 1391-7.

84. Kuendgen A, Nomdedeu M, Tuechler H, et al. Therapy-related myelodysplastic syndromes deserve specific diagnostic sub-classification and risk-stratification-an approach to classification of patients with t-MDS. *Leukemia* 2021; **35**(3): 835-49.
85. Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2021; **39**(11): 1223-33.
86. Nazha A, Komrokji R, Meggendorfer M, et al. Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2021; **39**(33): 3737-46.
87. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *The New England journal of medicine* 2011; **364**(26): 2496-506.
88. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. 2022; **1**(7): EVIDoa2200008.
89. Sauta E, Robin M, Bersanelli M, et al. Real-World Validation of Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2023: JCO2201784.
90. Kuendgen A, Strupp C, Aivado M, et al. Myelodysplastic syndromes in patients younger than age 50. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(34): 5358-65.
91. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica* 2011; **96**(3): 441-9.
92. Zipperer E, Pelz D, Nachtkamp K, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. *Haematologica* 2009; **94**(5): 729-32.
93. Sperr WR, Wimazal F, Kundi M, et al. Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2010; **21**(1): 114-9.
94. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007; **25**(27): 4246-54.
95. Starkman R, Alibhai S, Wells RA, et al. An MDS-specific frailty index based on cumulative deficits adds independent prognostic information to clinical prognostic scoring. *Leukemia* 2020; **34**(5): 1394-406.
96. Saber W, Horowitz MM. Transplantation for myelodysplastic syndromes: who, when, and which conditioning regimens. *Hematology Am Soc Hematol Educ Program* 2016; **2016**(1): 478-84.
97. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood* 2017; **129**(13): 1753-62.

98. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; **122**(17): 2943-64.
99. Fenaux P, Haase D, Santini V, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(dagger☆). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2021; **32**(2): 142-56.
100. Jadersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood* 2005; **106**(3): 803-11.
101. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. *Blood* 2008; **111**(2): 574-82.
102. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *British journal of haematology* 2003; **120**(6): 1037-46.
103. Garelius HK, Johnston WT, Smith AG, et al. Erythropoiesis-stimulating agents significantly delay the onset of a regular transfusion need in nontransfused patients with lower-risk myelodysplastic syndrome. *Journal of internal medicine* 2017; **281**(3): 284-99.
104. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(21): 3607-13.
105. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *The New England journal of medicine* 2005; **352**(6): 549-57.
106. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *The New England journal of medicine* 2006; **355**(14): 1456-65.
107. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. *Blood* 2011; **118**(14): 3765-76.
108. Santini V, Almeida A, Giagounidis A, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016; **34**(25): 2988-96.
109. Gattermann N, Finelli C, Porta MD, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. *Leukemia research* 2010; **34**(9): 1143-50.
110. Oliva EN, Alati C, Santini V, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. *The Lancet Haematology* 2017; **4**(3): e127-e36.
111. Fenaux P, Muus P, Kantarjian H, et al. Romiplostim monotherapy in thrombocytopenic patients with myelodysplastic syndromes: long-term safety and efficacy. *British journal of haematology* 2017; **178**(6): 906-13.

112. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. *Cancer* 2014; **120**(12): 1838-46.
113. Kantarjian HM, Fenaux P, Sekeres MA, et al. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomised double-blind trial. *The Lancet Haematology* 2018; **5**(3): e117-e26.
114. Oliva EN, Riva M, Niscola P, et al. Eltrombopag for Low-Risk Myelodysplastic Syndromes With Thrombocytopenia: Interim Results of a Phase-II, Randomized, Placebo-Controlled Clinical Trial (EQOL-MDS). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2023: JCO2202699.
115. Dickinson M, Cherif H, Fenaux P, et al. Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia. *Blood* 2018; **132**(25): 2629-38.
116. Platzbecker U. Treatment of MDS. *Blood* 2019; **133**(10): 1096-107.
117. 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. *The Lancet Oncology* 2009; **10**(3): 223-32.
118. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(36): 4533-40.
119. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *The New England journal of medicine* 2020; **382**(2): 140-51.
120. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. *Lancet* 2023.
121. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *The New England journal of medicine* 2020; **383**(7): 617-29.
122. Bazinet A, Darbaniyan F, Jabbour E, et al. Azacitidine plus venetoclax in patients with high-risk myelodysplastic syndromes or chronic myelomonocytic leukaemia: phase 1 results of a single-centre, dose-escalation, dose-expansion, phase 1-2 study. *The Lancet Haematology* 2022; **9**(10): e756-e65.
123. Zeidan AM, Borate U, Pollyea DA, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. *American journal of hematology* 2023; **98**(2): 272-81.
124. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010; **116**(19): 3724-34.
125. Benzarti S, Daskalakis M, Feller A, et al. Trends of incidence and survival of patients with chronic myelomonocytic leukemia between 1999 and 2014: A comparison between Swiss and American population-based cancer registries. *Cancer epidemiology* 2019; **59**: 51-7.

126. Onida F, Kantarjian HM, Smith TL, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. *Blood* 2002; **99**(3): 840-9.
127. Such E, Germing U, Malcovati L, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. *Blood* 2013; **121**(15): 3005-15.
128. Patnaik MM, Tefferi A. Chronic Myelomonocytic leukemia: 2020 update on diagnosis, risk stratification and management. *American journal of hematology* 2020; **95**(1): 97-115.
129. Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical chronic myelomonocytic leukemia (CMML), CMML variants and pre-CMML conditions. *Haematologica* 2019; **104**(10): 1935-49.
130. Itzykson R, Fenaux P, Bowen D, et al. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults: Recommendations From the European Hematology Association and the European LeukemiaNet. *HemaSphere* 2018; **2**(6): e150.
131. Selimoglu-Buet D, Wagner-Ballon O, Saada V, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. *Blood* 2015; **125**(23): 3618-26.
132. Patnaik MM, Timm MM, Vallapureddy R, et al. Flow cytometry based monocyte subset analysis accurately distinguishes chronic myelomonocytic leukemia from myeloproliferative neoplasms with associated monocytosis. *Blood cancer journal* 2017; **7**(7): e584.
133. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *British journal of haematology* 1976; **33**(4): 451-8.
134. Bennett JM, Catovsky D, Daniel MT, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group. *British journal of haematology* 1994; **87**(4): 746-54.
135. Such E, Cervera J, Costa D, et al. Cytogenetic risk stratification in chronic myelomonocytic leukemia. *Haematologica* 2011; **96**(3): 375-83.
136. Patnaik MM, Padron E, LaBorde RR, et al. Mayo prognostic model for WHO-defined chronic myelomonocytic leukemia: ASXL1 and spliceosome component mutations and outcomes. *Leukemia* 2013; **27**(7): 1504-10.
137. Malcovati L, Papaemmanuil E, Ambaglio I, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. *Blood* 2014; **124**(9): 1513-21.
138. Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. *Leukemia* 2014; **28**(11): 2206-12.
139. Patel BJ, Przychodzen B, Thota S, et al. Genomic determinants of chronic myelomonocytic leukemia. *Leukemia* 2017; **31**(12): 2815-23.
140. Patnaik MM, Lasho TL, Vijayvargiya P, et al. Prognostic interaction between ASXL1 and TET2 mutations in chronic myelomonocytic leukemia. *Blood cancer journal* 2016; **6**: e385.
141. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(19): 2428-36.

142. Elena C, Galli A, Such E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. *Blood* 2016; **128**(10): 1408-17.
143. Itzykson R, Solary E. An evolutionary perspective on chronic myelomonocytic leukemia. *Leukemia* 2013; **27**(7): 1441-50.
144. Itzykson R, Kosmider O, Renneville A, et al. Clonal architecture of chronic myelomonocytic leukemias. *Blood* 2013; **121**(12): 2186-98.
145. Wassie EA, Itzykson R, Lasho TL, et al. Molecular and prognostic correlates of cytogenetic abnormalities in chronic myelomonocytic leukemia: a Mayo Clinic-French Consortium Study. *American journal of hematology* 2014; **89**(12): 1111-5.
146. Elbaek MV, Sorensen AL, Hasselbalch HC. Chronic inflammation and autoimmunity as risk factors for the development of chronic myelomonocytic leukemia? *Leukemia & lymphoma* 2016; **57**(8): 1793-9.
147. Zahid MF, Barraco D, Lasho TL, et al. Spectrum of autoimmune diseases and systemic inflammatory syndromes in patients with chronic myelomonocytic leukemia. *Leukemia & lymphoma* 2017; **58**(6): 1488-93.
148. Santini V, Allione B, Zini G, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. *Leukemia* 2018; **32**(2): 413-8.
149. Aribi A, Borthakur G, Ravandi F, et al. Activity of decitabine, a hypomethylating agent, in chronic myelomonocytic leukemia. *Cancer* 2007; **109**(4): 713-7.
150. Pleyer L, Germing U, Sperr WR, et al. Azacitidine in CMML: matched-pair analyses of daily-life patients reveal modest effects on clinical course and survival. *Leukemia research* 2014; **38**(4): 475-83.
151. Braun T, Itzykson R, Renneville A, et al. Molecular predictors of response to decitabine in advanced chronic myelomonocytic leukemia: a phase 2 trial. *Blood* 2011; **118**(14): 3824-31.
152. Wattel E, Guerci A, Hecquet B, et al. A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Francais des Myelodysplasies and European CMML Group. *Blood* 1996; **88**(7): 2480-7.
153. Pleyer L, Leisch M, Kourakli A, et al. Outcomes of patients with chronic myelomonocytic leukaemia treated with non-curative therapies: a retrospective cohort study. *The Lancet Haematology* 2021; **8**(2): e135-e48.
154. Itzykson R, Santini V, Thepot S, et al. Decitabine Versus Hydroxyurea for Advanced Proliferative Chronic Myelomonocytic Leukemia: Results of a Randomized Phase III Trial Within the EMSCO Network. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2023; **41**(10): 1888-97.
155. Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. *Best practice & research Clinical haematology* 2013; **26**(4): 309-17.
156. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nature reviews Cancer* 2017; **17**(9): 513-27.
157. Nilsson C, Linde F, Hulegardh E, et al. Characterization of therapy-related acute myeloid leukemia: increasing incidence and prognostic implications. *Haematologica* 2023; **108**(4): 1015-25.

158. Morton LM, Dores GM, Schonfeld SJ, et al. Association of Chemotherapy for Solid Tumors With Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era. *JAMA oncology* 2019; **5**(3): 318-25.
159. Lange RD, Moloney WC, Yamawaki T. Leukemia in atomic bomb survivors. I. General observations. *Blood* 1954; **9**(6): 574-85.
160. Nardi V, Winkfield KM, Ok CY, et al. Acute myeloid leukemia and myelodysplastic syndromes after radiation therapy are similar to de novo disease and differ from other therapy-related myeloid neoplasms. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(19): 2340-7.
161. Ha H, Kim HJ, Park JH, et al. Epidemiologic outlook of therapy-related myeloid neoplasms and selection of high-risk patients: A Korean nationwide study. *Cancer* 2022; **128**(21): 3888-96.
162. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature* 2015; **518**(7540): 552-5.
163. Takahashi K, Wang F, Kantarjian H, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. *The Lancet Oncology* 2017; **18**(1): 100-11.
164. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. *The Lancet Oncology* 2017; **18**(1): 112-21.
165. Bolton KL, Ptashkin RN, Gao T, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nature genetics* 2020; **52**(11): 1219-26.
166. Jahn J, Diamond B, Hsu J, et al. Therapy-selected clonal hematopoiesis and its role in myeloid neoplasms. *Leukemia research* 2023; **126**: 107020.
167. Allen L, Williams J, Townsend N, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. *Lancet Glob Health* 2017; **5**(3): e277-e89.
168. Bjornerud Korslund S, Hansen BH, Bjorkkjaer T. Association between sociodemographic determinants and health behaviors, and clustering of health risk behaviors among 28,047 adults: a cross-sectional study among adults from the general Norwegian population. *BMC public health* 2023; **23**(1): 541.
169. Stringhini S, Sabia S, Shipley M, et al. Association of socioeconomic position with health behaviors and mortality. *Jama* 2010; **303**(12): 1159-66.
170. van Rossum CT, Shipley MJ, van de Mheen H, Grobbee DE, Marmot MG. Employment grade differences in cause specific mortality. A 25 year follow up of civil servants from the first Whitehall study. *J Epidemiol Community Health* 2000; **54**(3): 178-84.
171. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet* 2017; **389**(10075): 1229-37.
172. The Lancet Regional H-E. Sweden's economic inequality gap is widening and worrying. *Lancet Reg Health Eur* 2023; **26**: 100610.
173. Vaccarella S, Georges D, Bray F, et al. Socioeconomic inequalities in cancer mortality between and within countries in Europe: a population-based study. *Lancet Reg Health Eur* 2023; **25**: 100551.

174. Larfors G, Sandin F, Richter J, et al. The impact of socio-economic factors on treatment choice and mortality in chronic myeloid leukaemia. *European journal of haematology* 2017; **98**(4): 398-406.
175. Ostgard LSG, Norgaard M, Medeiros BC, et al. Effects of Education and Income on Treatment and Outcome in Patients With Acute Myeloid Leukemia in a Tax-Supported Health Care System: A National Population-Based Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017; **35**(32): 3678-87.
176. Kristinsson SY, Derolf AR, Edgren G, Dickman PW, Bjorkholm M. Socioeconomic differences in patient survival are increasing for acute myeloid leukemia and multiple myeloma in sweden. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(12): 2073-80.
177. Biasoli I, Castro N, Delamain M, et al. Lower socioeconomic status is independently associated with shorter survival in Hodgkin Lymphoma patients-An analysis from the Brazilian Hodgkin Lymphoma Registry. *International journal of cancer* 2018; **142**(5): 883-90.
178. Tao L, Foran JM, Clarke CA, Gomez SL, Keegan TH. Socioeconomic disparities in mortality after diffuse large B-cell lymphoma in the modern treatment era. *Blood* 2014; **123**(23): 3553-62.
179. Baker KS, Davies SM, Majhail NS, et al. Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2009; **15**(12): 1543-54.
180. Jabo B, Morgan JW, Martinez ME, Ghamsary M, Wieduwilt MJ. Sociodemographic disparities in chemotherapy and hematopoietic cell transplantation utilization among adult acute lymphoblastic and acute myeloid leukemia patients. *PloS one* 2017; **12**(4): e0174760.
181. Wang R, Gross CP, Halene S, Ma X. Neighborhood socioeconomic status influences the survival of elderly patients with myelodysplastic syndromes in the United States. *Cancer causes & control : CCC* 2009; **20**(8): 1369-76.
182. England JT, Zhang L, Buckstein R, et al. Income and outcome in myelodysplastic syndrome: the prognostic impact of SES in a single-payer system. *Leukemia research* 2013; **37**(11): 1495-501.
183. Mastaglio F, Bedair K, Papaemmanuil E, et al. Impact of socioeconomic status on disease phenotype, genomic landscape and outcomes in myelodysplastic syndromes. *British journal of haematology* 2016; **174**(2): 227-34.
184. Lauritsen TB, Ostgard LSG, Gronbaek K, Dalton SO, Norgaard JM. Socioeconomic position and clinical outcomes in patients with myelodysplastic syndromes: A population-based cohort study. *Hematol Oncol* 2022; **40**(5): 1056-66.
185. Smith AR, Warlick ED, Roesler MA, et al. Factors associated with hematopoietic cell transplantation (HCT) among patients in a population-based study of myelodysplastic syndrome (MDS) in Minnesota. *Annals of hematology* 2015; **94**(10): 1667-75.
186. Abel GA, Cronin AM, Odejide OO, Uno H, Stone RM, Steensma DP. Influence of patient and provider characteristics on quality of care for the myelodysplastic syndromes. *British journal of haematology* 2016; **173**(5): 713-21.
187. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC public health* 2011; **11**: 450.
188. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009; **48**(1): 27-33.

189. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety* 2007; **16**(7): 726-35.
190. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017; **32**(9): 765-73.
191. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol* 2019; **34**(4): 423-37.
192. Armitage JN, van der Meulen JH, Royal College of Surgeons Co-morbidity Consensus G. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg* 2010; **97**(5): 772-81.
193. Ludvigsson JF, Appelros P, Askling J, et al. Adaptation of the Charlson Comorbidity Index for Register-Based Research in Sweden. *Clin Epidemiol* 2021; **13**: 21-41.
194. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika* 1994; **81**(3): 515-26.
195. Harrell FE, Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *Jama* 1982; **247**(18): 2543-6.
196. Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. *Statistics in medicine* 2015; **34**(4): 685-703.
197. Peker D, Padron E, Bennett JM, et al. A close association of autoimmune-mediated processes and autoimmune disorders with chronic myelomonocytic leukemia: observation from a single institution. *Acta haematologica* 2015; **133**(2): 249-56.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1963

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-508646

ACTA UNIVERSITATIS
UPSALIENSIS
2023