Characterization of therapy-related acute myeloid leukemia: increasing incidence and prognostic implications

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Received: April 18, 2022.
Accepted: July 21, 2022.
Early view: August 25, 2022.

https://doi.org/10.3324/haematol.2022.281233

Abstract

Studies of therapy-related AML (t-AML) are usually performed in selected cohorts and reliable incidence rates are lacking. In this study, we characterized, defined the incidence over time and studied prognostic implications in all t-AML patients diagnosed in Sweden between 1997 and 2015. Data were retrieved from nationwide population-based registries. In total, 6,779 AML patients were included in the study, of whom 686 (10%) had t-AML. The median age for t-AML was 71 years and 392 (57%) patients were females. During the study period, the incidence of t-AML almost doubled with a yearly increase in t-AML of 4.5% (95% confidence interval: 2.8%-6.2%), which contributed significantly to the general increase in AML incidence over the study period. t-AML solidly constituted over 10% of all AML cases during the later period of the study. Primary diagnoses with the largest increase in incidence and decrease in mortality rate during the study period (i.e., breast and prostate cancer) contributed significantly to the increased incidence of t-AML. In multivariable analysis, t-AML was associated with poorer outcome in cytogenetically intermediate- and adverse-risk cases but t-AML had no significant impact on outcome in favorable-risk AML, including core binding leukemias, acute promyelocytic leukemia and AML with mutated *NPM1* without *FLT3*-ITD. We conclude that there is a strong increase in incidence in t-AML over time and that t-AML constitutes a successively larger proportion of the AML cases. Furthermore, we conclude that t-AML confers a poor prognosis in cytogenetically intermediate- and adverse-risk, but not in favorable-risk AML.

Introduction

Therapy-related AML (t-AML) is a feared complication of treatment with chemotherapy and/or radiation. The World Health Organization (WHO) defines the disease entity therapy-related myeloid neoplasms as myeloid neoplasms secondary to cytotoxic treatment, in which t-AML is categorized along with therapy-related myelodysplastic syndrome (MDS) and therapy-related myeloproliferative neoplasms (MPN).[1] Between 5-10% of all AML cases have been reported to be therapy-related,[2,3] and treatment for a solid cancer increases the risk of AML up to 10-fold with chemotherapy[4] and 2.5-fold after treatment with radiotherapy.[5] While solid and hematologic tumors dominate as the primary disease, t-AML may also occur after treatment of non-malignant diseases, especially inflammatory disorders.[3,6-8] The mechanism behind the increased risk of AML after chemo- and/or radiation therapy are not fully understood, but it is currently regarded as a combination of mutagenic effects of chemotherapy and/or radiation and a selective pressure by this treatment, favoring existing premalignant clones in the blood and bone marrow.[9-13] This may lead to clonal expansion of the premalignant clone as well as clonal evolution with accumulation of additional leukemogenic genetic aberrations that evolve to t-AML.
t-AML is associated with a worse prognosis compared to that of *de novo* AML, and the disease presents with a higher rate of adverse genetic aberrations compared to *de novo* AML.[3] Alkylating agents and radiation therapy have typically been associated with aberrations in chromosomes 5 and 7, while treatment with topoisomerase II inhibitors has been linked to rearrangements of

chromosome 11q23, involving the *KMT2A* gene.[14] However, as chemotherapy treatment usually consists of a combination of agents, this subdivision of t-AML is difficult to identify clinically, and it is no longer part of the WHO classification.[15] Complex and monosomal karyotypes as well as *TP53* mutations are also overrepresented in t-AML.[7,16,17]

The spectrum of tumors that precedes t-AML depends on incidence rates, type of treatment and the likelihood of long-term survival for the particular cancer type.[4,18] Thus, tumors treated with high intensity chemotherapy followed by high cure rates, are overrepresented as pre-t-AML diagnoses.[3,19] Consequently, malignancies that are less frequently treated with intensive chemotherapy, such as prostate cancer, or malignancies with short survival are generally underrepresented as primary diseases in t-AML.[3,20]

Most studies of t-AML are either small or performed in selected cohorts and within clinical trials. Larger population-based studies in which t-AML is defined from a real-life perspective, and from which true incidence rates can be calculated, are exceedingly rare. Here, we use population-based quality registries in Sweden to investigate changes in incidence and survival in t-AML over time, as well as to characterize t-AML in a large real-life AML cohort. Furthermore, we study prognostic factors for t-AML patients, as well as t-AML in itself as a prognostic factor within genetic subtypes of AML.

Methods

Data collection

Data were collected from three nationwide registries: the Swedish AML Registry (SAMLR), the Swedish Cancer Registry (SCR) and the Swedish Rheumatology Quality Register (SRQ). SAMLR has been validated against the SCR defining the coverage of SAMLR to 98% of all AML patients nationwide.[21] Each registry, its data and the methods to collect data are described in more detail in the *Online Supplementary Methods*. All registries use national unique personal identification numbers enabling identification of individuals across the registries.

Patients

The study included all AML patients ≥8 years reported to SAMLR between January 1, 1997 and December 31, 2015. Two t-AML patients with a prior AML diagnosis reported as the antecedent disease were excluded. The median follow-up time was 101 months during which 4,406 deaths were registered; 10 patients were lost to follow-up and 1,076 patients were still alive at the end of follow-up. Intensively treated patients received induction and consolidation therapy according to Swedish guidelines,[22] with a chemotherapy intensity comparable to that of the classical "3 + 7" AML induction. The ethical review board in Gothenburg approved the study (Dnr 781/13).

Definitions

t-AML was defined as AML with a prior diagnosis of a malignant or non-malignant disease treated with chemotherapy and/or radiation therapy. All chemotherapy regimens were considered, including methotrexate and cyclophosphamide for autoimmune diseases, but excluding immunosuppressive treatment. Patients treated with chemotherapy for MDS or MPN and progressing to AML were not defined as therapy-related cases, whereas patients developing MDS or MPN during the period between the treatment for the primary disease and the diagnosis of AML were considered to have t-AML. The 2010 European LeukemiaNet (ELN) criteria[23] were used to stratify patients into cytogenetic risk groups. For risk classification of patients with available data on *NPM1* and *FLT3*-ITD mutational status (starting from 2007) the ELN2010 criteria for *NPM1* and *FLT3*-ITD were used. Complete remission was defined as <5% blasts in the bone marrow and recovery of peripheral blood counts.

Statistical analyses

Between-group comparisons of categorical and continuous variables were performed using the Pearson χ^2 test and the Mann-Whitney U test, respectively. The unequal variances *t* test was used to compare mean incidence rates between time periods. Overall survival was estimated using the Kaplan-Meier method and compared with the log-rank test or univariable Cox regression. Multivariable Cox regression was used for survival analyses with covariates specified where used. The proportional hazards assumption was tested for each covariate by graphical inspection of the scaled Schoenfeld residuals. Two-tailed tests with a 0.05 level of significance were used throughout the analyses. No imputation of missing data was performed. All data preparation and statistical analyses were conducted in R, version 3.6.0.[24] Additional information about the statistical methods can be found in the *Online Supplementary Material*.

Results

Patients' characteristics

A total of 5,492 patients were diagnosed with either t-AML (n=686) or *de novo* AML (n=4,806) in Sweden between 1997 and 2015, with an additional 1,287 patients being diagnosed with AML with an antecedent hematologic disease (AHD-AML). The aim of this study was to characterize t-AML patients specifically, which is why details on AHD-AML patients are not further described. Of all AML cases in the study cohort, the proportion of t-AML was 10%, *de novo* AML 71% and AHD-AML 19%.

The clinical characteristics of patients with t-AML and *de novo* AML are shown in Table 1. Age at diagnosis was similar between t-AML and *de novo* AML (median 71 *vs*. 70 years, respectively) while t-AML had a female predominance (57%, compared to 49% in *de novo* AML). Performance status was similar with the majority of patients having Eastern Cooperative Oncology Group grade 0 or 1 (61% *vs*. 63%, t-AML and *de novo* AML, respectively). Adverse cytogenetic risk was more common (46% *vs*. 28%, *P*<0.001) in t-AML, while favorable risk was somewhat less common (12% *vs*. 16%, *P*=0.030). The proportion of APL was similar in t-AML compared to *de novo* AML (4% *vs*. 5%). Minor differences were observed in standard clinical parameters, with patients with t-AML having lower median bone marrow blast percentages (46% *vs*. 50%), lower white blood cell counts (6.1 *vs*. 8.7x10^9/L) and lower platelet counts (50 *vs*. 65 x10^9/L) compared to those with *de novo* AML. Inflammatory diseases and unspecified chronic diseases were more prevalent in t-AML than in *de novo* AML (13% *vs*. 3% and 23% *vs*. 9%, respectively), while the prevalence

Table 1. Clinical characteristics of patients with therapy-related acute myeloid leukemia and *de novo* acute myeloid leukemia.

	Overall	*De novo* AML	t-AML	*P*
N of patients	5,492	4,806	686	
Age at diagnosis in years, median (range)	70 (18-100)	70 (18-98)	71 (18-98)	0.519
Female, N (%)	2,743 (50)	2,351 (49)	392 (57)	<0.001
Year of diagnosis, N (%)				<0.001
1997-2002	1,621 (30)	1,455 (30)	166 (24)	
2003-2008	1,672 (30)	1,487 (31)	185 (27)	
2009-2015	2,199 (40)	1,864 (39)	335 (49)	
ECOG performance status, N (%)				0.079
0	1,086 (20)	980 (21)	106 (16)	
1	2,308 (42)	2,005 (42)	303 (45)	
2	953 (17)	825 (17)	128 (19)	
3	607 (11)	524 (11)	83 (12)	
4	361 (7)	317 (7)	44 (6)	
Missing	134 (2)	118 (2)	16 (2)	
Cytogenetic risk, N (%) (data reported on 73% of cases)				<0.001
Adverse	1,201 (30)	964 (28)	237 (46)	
Intermediate	2,187 (55)	1,974 (56)	213 (42)	
Favorable	619 (15)	559 (16)	60 (12)	
FLT3-ITD, N (%) (data reported on 23% of cases)				0.053
Present	316 (25)	295 (26)	21 (18)	
Absent	927 (75)	829 (74)	98 (82)	
NPM1, N (%) (data reported on 21% of cases)				0.172
Present	348 (30)	321 (31)	27 (24)	
Absent	805 (70)	720 (69)	85 (76)	
CEBPA, N (%) (data reported on 7% of cases)				0.709
Present	27 (7)	25 (8)	2 (5)	
Absent	348 (93)	307 (92)	41 (95)	
APL, N (%)	250 (5)	224 (5)	26 (4)	0.355
Treatment, N (%)				<0.001
Hypomethylating agent	89 (2)	61 (1)	28 (4)	
Intensive	3,590 (70)	3,205 (71)	385 (60)	
None/palliative	1,485 (29)	1,251 (28)	234 (36)	
CR, intensively treated, N (%)	2,617 (73)	2,393 (75)	224 (58)	<0.001
Allogeneic HCT, N (%)				0.001
In CR1	606 (11)	555 (12)	51 (7)	
In > CR1, relapsed or refractory state	208 (4)	191 (4)	17 (2)	
No	4,678 (85)	4,060 (84)	618 (90)	

Note: Data on F*LT3*-ITD, *NPM1*, *CEBPA*, comorbidities and blood chemistry are only reported since 2007. AML: acute myeloid leukemia; t-AML: therapy-related AML; ECOG: Eastern Cooperative Oncology Group; APL: acute promyelocytic leukemia; CR: complete remission; HCT: allogeneic hematopoietic stem cell transplantation; CR1: first complete remission.

of other comorbidities was similar (*Online Supplementary Table S1*).

Patients with t-AML were less likely to receive intensive induction treatment (60% *vs*. 71%, *P*<0.001) and intensively treated patients were less likely to reach complete remission (58% *vs*. 75%; *P*<0.001) compared to those with *de novo* AML. Allogeneic hematopoietic cell transplantation (HCT), regardless of disease state, was performed in 9% of the patients with t-AML compared to 16% of those with *de novo* AML (*P*<0.001). Corresponding rates of HCT in first remission were 7% in t-AML compared to 12% in *de novo* AML (*P*=0.002). There was no increase or decrease of transplantation rates over time (*data not shown*).

The incidence of therapy-related acute myeloid leukemia is increasing over time

The age-standardized incidence rate of t-AML increased during the study period from a mean of 0.39 cases per 100,000 adult inhabitants between 1997 and 2006 to 0.63 between 2007 and 2015 (*P*=0.004) (Figure 1A). During the last 2 years of the study period (2014-2015), the average age-adjusted incidence rate of t-AML was 0.95. There was also a slight increase in the incidence of *de novo* AML from 3.42 to 3.66 between the two study periods (*P*=0.02). For all AML (including *de novo* AML, t-AML and AHD-AML), the incidence rate increased from 4.69 (1997-2006) to 5.32 (2007-2015) (*P*=0.0006). The estimated annual percentage change was 4.5 % in t-AML (95% confidence interval [95% CI]: 2.8%-6.2%) compared to 0.7% in *de novo* AML (95% CI: 0.2%-1.2%). The relative increase in t-AML was substantial and contributed to a large proportion of the increased incidence of AML as a whole. As a result, the proportion of t-AML of all AML cases increased from 8.3% in 1997-2006 to 11.8% in 2007-2015 (*P*=0.004, *t* test) (Figure 1B). For the last 2 years of the study period (2014-2015), the average proportion of t-AML was 16%.

To define how different primary tumors contributed to the increase in t-AML incidence, we compared the average number of t-AML cases per year per primary tumor disease between 1997-2002 and 2009-2015. Non-malignant diseases, breast cancer and prostate cancer contributed most to the rise in t-AML incidence with an absolute increase of 8.2, 5.6 and 5.2 cases per year per 10 million inhabitants, representing 40%, 27% and 25% of the increase in t-AML, respectively. A slightly increased contribution was also seen for lymphoma and gastrointestinal cancers. In contrast, gynecological cancers and multiple myeloma displayed a relatively stable or decreased contribution to t-AML over time (*Online Supplementary Table S2* and *Online Supplementary Figure S1*). To understand the contribution of the different primary diagnoses, we used official data from the Swedish Cancer Registry to compare the change

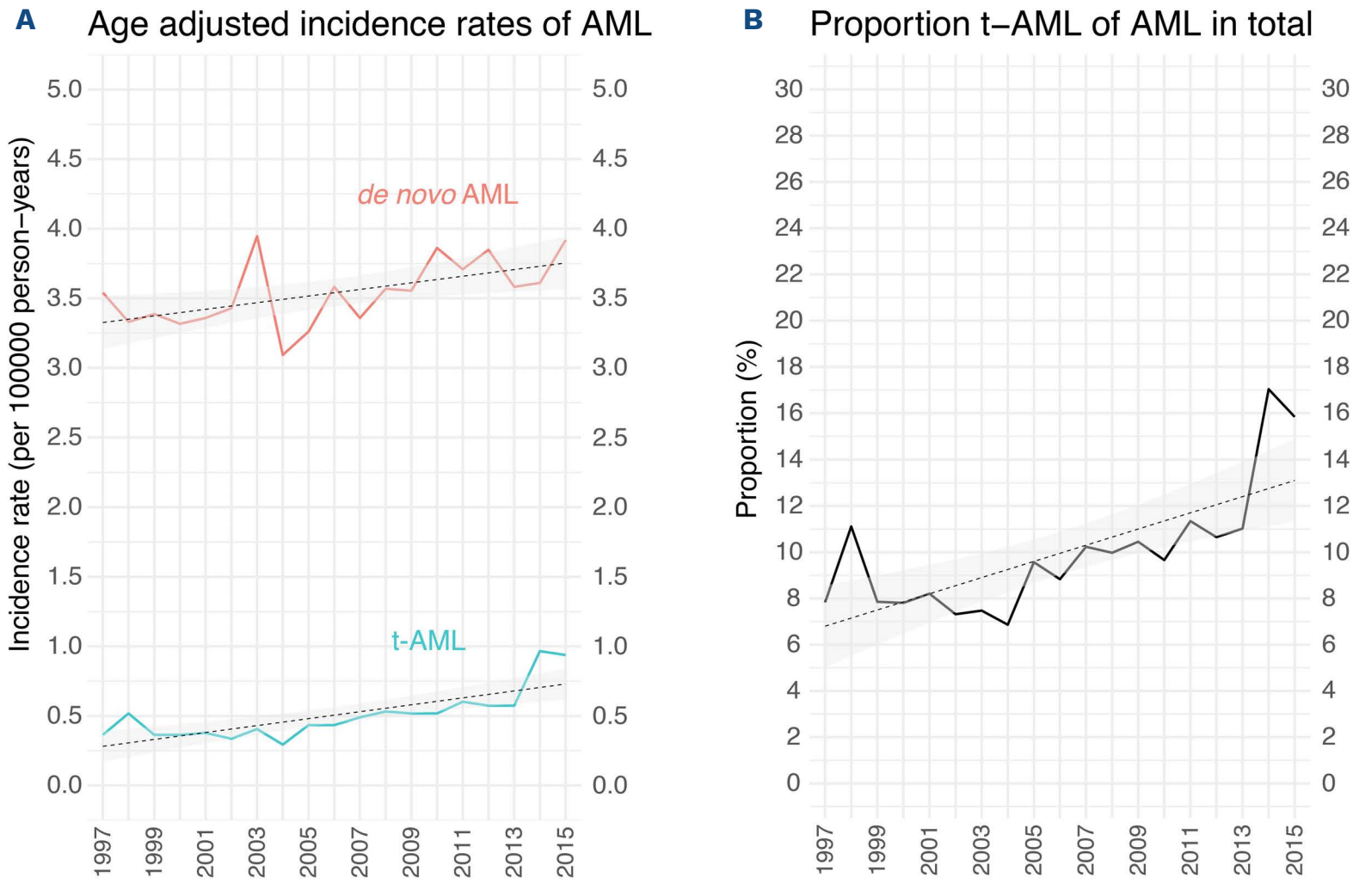
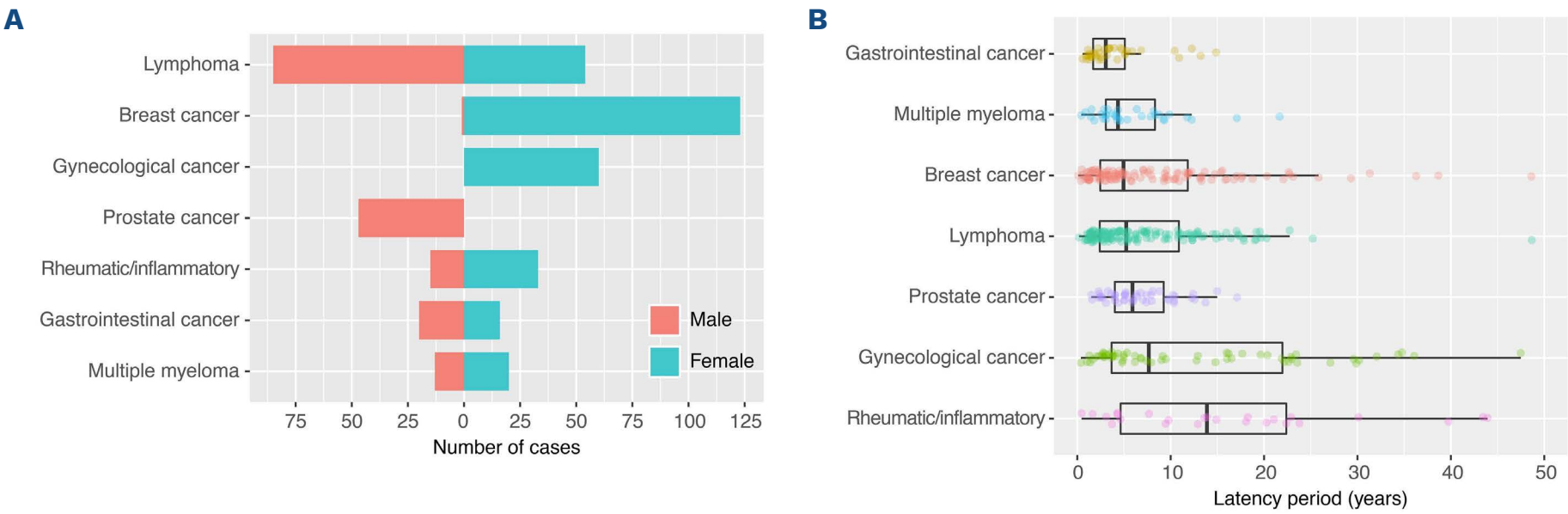


Figure 1. Incidence rates and proportion of therapy-related acute myeloid leukemias. (A) Age-standardized incidence rates of therapy-related acute myeloid leukemia (AML) and *de novo* AML. (B) Percentage of therapy-related AML cases of all AML cases. Figures show linear regression lines with 95% confidence intervals for visual aid.

in t-AML incidence to the change in incidence and mortality rate for the malignant diagnoses during the same period. As shown in *Online Supplementary Figure S2A-L*, the primary diagnoses that contributed most to the increase in t-AML, i.e. breast and prostate cancer, also displayed the largest increase in incidence and most prominent decrease in mortality rates. For gynecological cancers, incidence and mortality rates remained relatively unchanged for cervix and uterine corpus cancer while they decreased for ovarian carcinoma. Lymphoma displayed a small increase in incidence and a slightly improved survival. Thus, the increase in t-AML incidence seems to be at least partly driven by increased incidence and improved survival of some major tumors.

Characterization of diagnoses prior to therapy-related acute myeloid leukemia

Of primary disorders, for which chemotherapy and/or radiation was given, 55% were non-hematologic solid cancers, 25% hematologic cancers and 18% non-malignant diseases. Figure 2A shows the number of cases and the gender distribution for each primary diagnosis and more details are provided in *Online Supplementary Table S3*. The most common primary diagnoses were lymphoma (n=139), followed by breast cancer (n=124), rheumatic and inflammatory disease (n=122), gynecological malignancies (n=60), prostate cancer (n=47), gastrointestinal cancer (n=36), and myeloma (n=33). Treatment for the primary disease was chemotherapy alone in 49%, radiation therapy alone in 25%, and chemotherapy and radiation therapy combined in 26% of the patients (*Online Supplementary Table S3*).



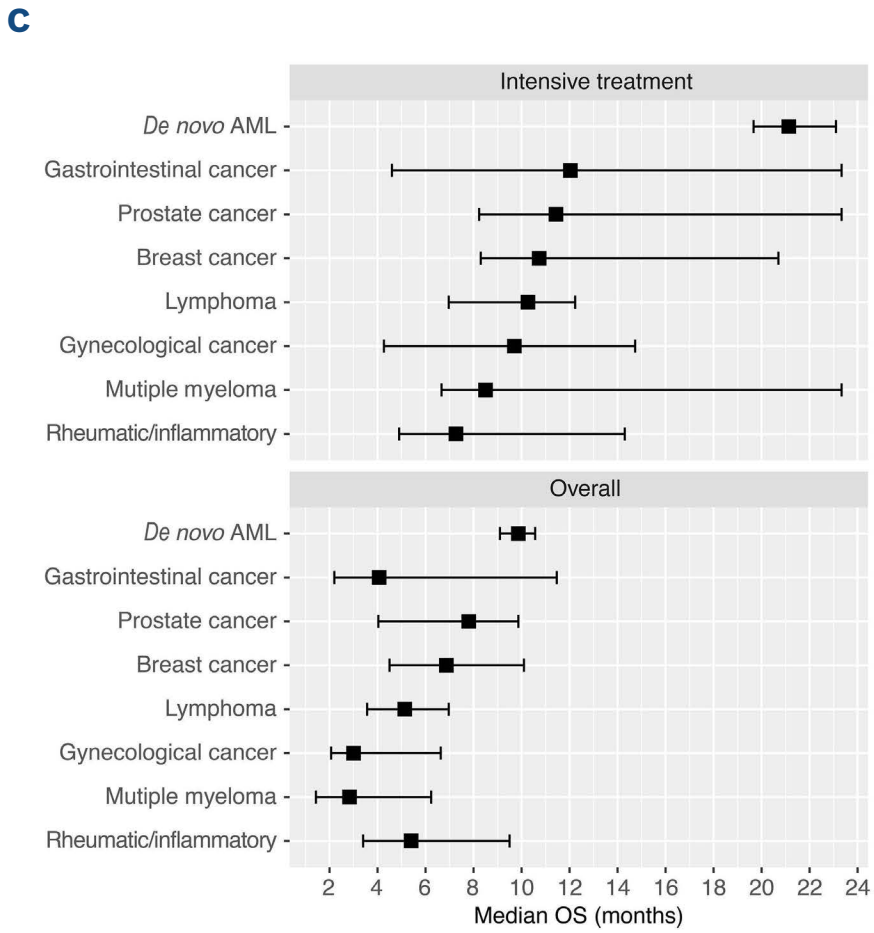


Figure 2. Primary diagnosis, gender, latency times and survival in therapy-related acute myeloid leukemia. (A) Number of cases and gender based on primary diagnoses. (B) Latencies between diagnosis of the primary disease and acute myeloid leukemia related to different primary diagnoses. (C) Median overall survival in intensively treated patients and overall in therapy-related acute myeloid leukemia grouped by primary disease. AML: acute myeloid leukemia; t-AML: therapy-related acute myeloid leukemia;

Nineteen percent (n=133) of t-AML patients had more than one tumor diagnosis before the onset of t-AML, either occurring before, or more often after the malignancy for which the first chemotherapy and/or radiation therapy was given. Figure 3 displays in detail the complexity of sequential relations between the different diagnoses. Seventeen percent (n=118) of the patients had a diagnosis of MDS between the primary disease and t-AML.

Latency periods

The latency period after a primary hematologic malignancy or a solid cancer to the diagnosis of t-AML was similar (median 57 *vs.* 61 months, respectively; *P*=0.287) while the latency period after diagnosis of a primary non-malignant disease (i.e., inflammatory or rheumatic disease) was longer (173 months; *P*<0.001), but also more variable (*Online Supplementary Figure S3*A). Figure 2B displays latency periods related to type of primary disease. The latency also varied with the type of primary treatment with similar la-

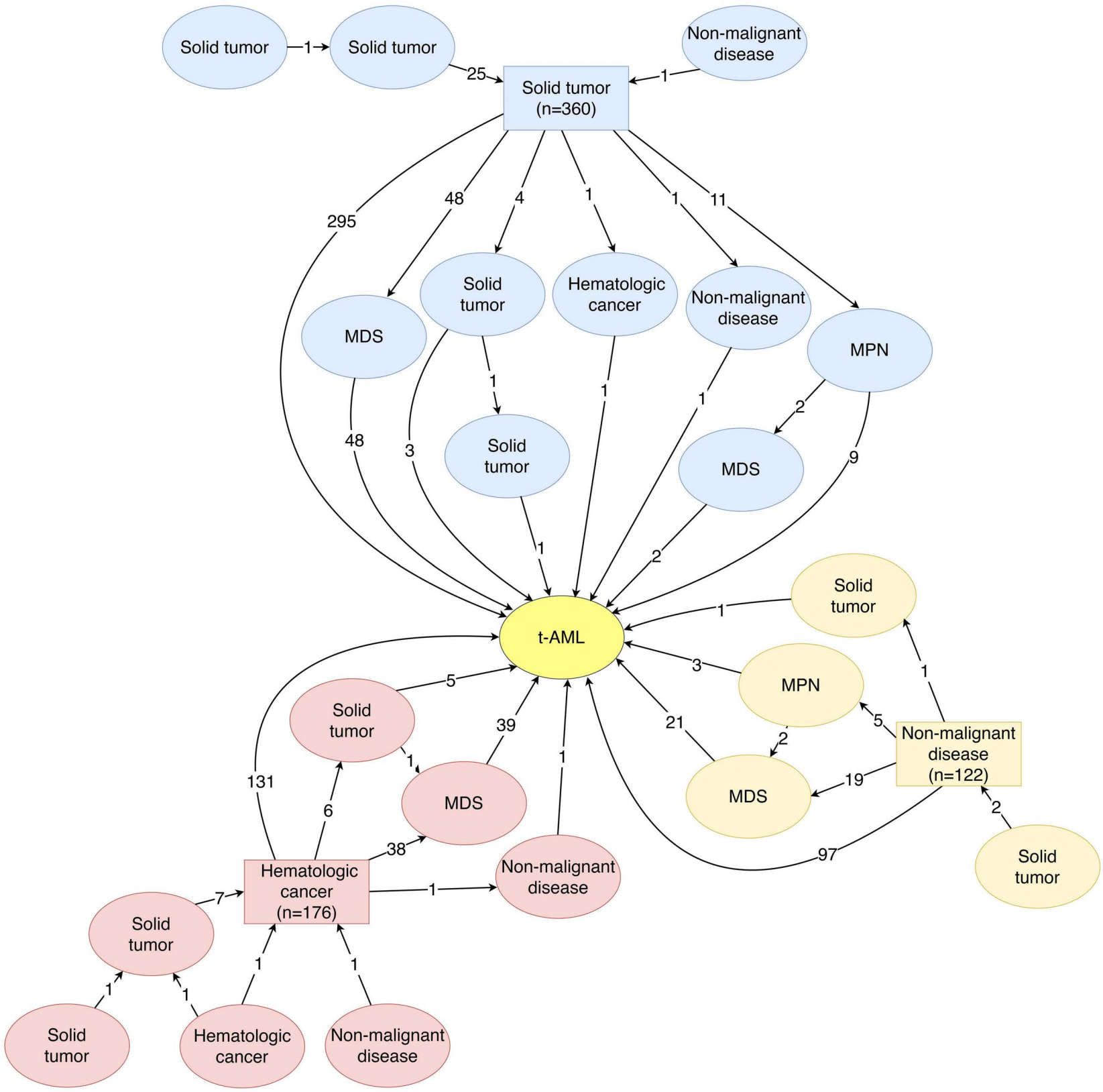


Figure 3. Paths to therapy-related acute myeloid leukemia. The figure shows the sequence of diagnoses of all malignant and/or hematologic diseases preceding the diagnosis of therapy-related acute myeloid leukemia (t-AML). Squares denote the primary disease for which cytotoxic treatment was given and ovals denote additional diseases, either prior to the primary disease or between the primary disease and t-AML. Numbers between squares and ovals represent number of cases. Twenty-eight cases for which the order of the disease could not be determined were excluded from the figure. MDS: myelodysplastic syndromes; MPN: myeloproliferative neoplasms.

tency after chemotherapy alone and combination therapy (chemotherapy + radiation) (median 54 *vs.* 55 months, respectively; *P*=0.848), but longer after radiation alone (median 97 months; *P*<0.001) (*Online Supplementary Figure S3B*). Both a primary non-malignant disease and radiation alone were associated with a longer latency period in multivariable analysis adjusting for age at primary diagnosis, type of primary treatment, type of primary disease and cytogenetic risk at diagnosis (*Online Supplementary Table S4*). The median latency periods of patients with -5/-7, 11q23/*MLL* and t(15;17) were 101 months (95% CI: 74-126 months), 41 months (95% CI: 29-75 months) and 84 months (95% CI: 41-190 months), respectively, compared to 62 months in t-AML overall (95% CI: 56-71 months). There was no association between the latency period and favorable, intermediate or adverse risk at large.

Improved survival for therapy-related acute myeloid leukemia patients over time

The estimated 5-year survival of patients with t-AML was 10% overall, 17% in intensively treated patients (n=385), and 48% in patients who underwent HCT (n=68). As a comparison, the 5-year survival rates in patients with *de novo* AML were 23% overall, 34% in intensively treated patients, and 57% in transplanted patients. Similarly, the median overall survival was 5.0 months for all t-AML, 9.5 months in intensively treated patients, and 48 months in patients who underwent HCT (*Online Supplementary Figure S4A-C*). Corresponding median overall survival times patients with *de novo* AML were 9.7 months overall, 20.7 months in intensively treated patients, and 113 months in transplanted patients. Overall survival among patients transplanted in first complete remission was worse in t-AML patients than in *de novo* AML patients in both univariable analysis (hazard ratio [HR]=1.56, 95% CI: 1.06-2.29) and after adjusting for age and cytogenetic risk (HR=1.50, 95% CI: 1.02-2.22).

Outcome of patients with t-AML improved over time with a 5-year overall survival in intensively treated patients of 11%, 16% and 23% for 1997-2002, 2003-2008 and 2009-2015, respectively *(Online Supplementary Figure S5A, B*). Patients with an antecedent diagnosis of MDS had a worse outcome in univariable analysis compared to patients without prior MDS (HR=1.52, 95% CI: 1.09-2.12, *P*=0.012) but when adjusting for age and cytogenetic risk, no significant survival difference was observed (*Online Supplementary Table S5*). Patients with t-AML did worse compared to those with *de novo* AML regardless of primary disease (Figure 2C, details in *Online Supplementary Table S6*) and type of treatment for the primary disease (chemotherapy, radiotherapy or chemo-radiotherapy; *Online Supplementary Figure S6A, B*). No correlation between the type of cytotoxic treatment and cytogenetic risk was found (distribution of risk in patients treated with radiotherapy only *vs.* patients treated with chemotherapy or combination therapy, *P*=0.06). The cumulative incidence of death and relapse was higher in patients older than 60 years, although the relapse difference was not statistically significant (*Online Supplementary Figure S7*).

Therapy-related acute myeloid leukemia had a strong negative impact on survival in cytogenetically intermediate- and adverse- but not favorable-risk acute myeloid leukemia

How t-AML contributes to prognosis within different AML risk groups remains unclear. Therefore, we analyzed the outcomes of patients with t-AML compared to those with *de novo* AML in each cytogenetic risk group. In crude analyses, t-AML did not have a statistically significant impact on outcome in favorable-risk AML, regardless of whether acute promyelocytic leukemia (APL) was included in the favorable-risk group or not. In contrast, there was a significant and strong negative impact of t-AML in intermediate- and adverse-risk AML (*Online Supplementary Figure S8A-E*). After adjusting for age and performance status, survival was still similar in favorable-risk t-AML (with or without APL) and in APL alone compared to *de novo* AML: HR=0.99 (*P*=0.95); HR=1.11 (*P*=0.73), and HR=0.89 (*P*=0.78), respectively. In contrast, after the same adjustments in the intermediate- and adverse-risk groups, t-AML had a strong negative impact on overall survival: HR=1.53 (*P*<0001) and HR=1.59 (*P*<0.001), respectively (Table 2).

Therapy-related acute myeloid leukemia does not confer poor prognosis in acute myeloid leukemia with mutated *NPM1* and absence of *FLT3*-ITD

We further analyzed the impact of *NPM1* mutations and *FLT3*-ITD (data available from 2007). There were 112 t-AML patients for whom information on *NPM1* status was available and 119 for whom *FLT3*-ITD data were available; among *de novo* AML patients, the corresponding numbers were 1,041 and 1,124 patients, respectively. In t-AML patients, *FLT3*-ITD alone did not add prognostic information (Figure 4A), while t-AML patients with *NPM1*^{mut} had significantly better overall survival compared to *NPM1*^{wt} t-AML patients (Figure 4B). t-AML patients with *NPM1*^{mut} in combination with *FLT3*^{wt} had better survival compared to t-AML patients with any other combination of *NPM1* and *FLT3* status (Figure 4C). t-AML patients with *NPM1*^{mut}/*FLT3*^{wt} had a similar overall survival compared to that of *NPM1*^{mut}/*FLT3*^{wt} *de novo* AML patients (HR=0.82, 95% CI: 0.40-1.68, *P*=0.584 for t-AML *vs. de novo* AML) (Figure 4D). The comparison showed similar results when adjusting for age, performance status and cytogenetic risk (t-AML *vs. de novo* AML: HR=0.75, 95% CI: 0.36-1.58, *P*=0.454).

The role of t-AML in relation to the ELN2017 classification including a more comprehensive mutational characterization was outside the scope of the study as the study was based on retrospective registry data from a period before

comprehensive mutational analyses was performed routinely. Nevertheless, full mutational characterization was available for 58 of the patients and these data are provided in *Online Supplementary Figure S9*.

Discussion

In this study, we identified several features of t-AML that point to important current trends regarding t-AML and that provide real-world information on the role of t-AML in the prognostic outcome of AML. Firstly, we identified a significant increase in the incidence of t-AML during the last two to three decades. This increase is substantial and approaches a doubling during the study period. Consequently, it is much more likely that a newly diagnosed AML is a t-AML today compared to 20 to 30 years ago. This increase in t-AML was seen for primary tumors that have shown an increased incidence and decreased mortality during the same period, such as breast and prostate cancers. This is in part due to improvement of cancer therapy, leading to better long-term survival after mutagenic cancer treatments.[25,26] With continuous improvements in survival of patients with malignant diseases, the number of individuals at risk of t-AML will continue to rise. However, the use of less mutagenic non-chemotherapeutic agents in cancer treatment may in part counteract this development.

Over the whole study period, the incidence of t-AML in our study was 0.51 cases per 100,000 inhabitants, which is substantially higher than that found in a recent American study using data from the Surveillance, Epidemiology, and End Results (SEER) registry in which the incidence rate of therapy-related myeloid neoplasms was 0.13 cases per 100,000 during 2001–2014.[19] The reason for the discrepancy is unclear. Although it may be related to differences concerning treatment and/or survival of malignancies in general, it more likely reflects a difference in reporting and coverage of the registries as well as their sensitivity and specificity for recording previous treatment with chemotherapy and radiation. The advantage of the Swedish reporting system is the 98% coverage of the Swedish AML Registry, the compulsory reporting of cancer diagnoses to the Swedish Cancer Registry and the possibility of cross-linking the registries for each individual using personal identification numbers.

Regarding the basic characterization of the t-AML patients in this study, it is in line with most previous studies[2,7,8] while we here can provide data from the largest population-based cohort of AML so far. The good performance status of t-AML patients is somewhat surprising, however, it is confirmed by several other studies.[27,28] The good performance status contrasts with the fact that t-AML patients were less likely to receive intensive chemotherapy and allogeneic transplantation. This could be due to fact that other factors rather than performance status can affect the treating physician's assessment of the patient, such as sequelae from previous exposure to chemotherapy or radiation as well as the presence of a still existing primary tumor. Regarding the latency periods, they were associated with factors such as type of treatment (chemotherapy or radiation) and type of primary disease (malignant *vs.* non-malignant). In line with previous studies, patients with 11q23/*MLL*-rearranged AML had shorter latency periods, while those with -5/-7 had longer latency periods.[7,29]

Secondly, we were able to examine and describe the role of t-AML in the prognosis within AML risk groups. It is well established that karyotype is an independent prognostic factor among intensively treated patients with t-AML and that poor-risk karyotypes are overrepresented in t-AML.[7,29,30] However, data on the impact of t-AML within each cytogenetic risk group are conflicting. Our data showed a significantly worse survival in t-AML patients within the intermediate and adverse AML risk groups. In contrast, t-AML patients with favorable-risk AML had the same survival as that of patients with *de novo* AML, also when correcting for other prognostic factors. Schoch *et al.* previously reported data contrasting with ours, with no

Table 2. Multivariable Cox regression analysis of overall survival in therapy-related acute myeloid leukemia compared to *de novo* AML in intensively treated patients according to cytogenetic risk.

		HR (95% CI)	*P*
Favorable risk			
APL excluded	t-AML *vs. de novo*	1.11 (0.62-1.97)	0.732
	Age	1.04 (1.03-1.06)	<0.001
	ECOG PS 2-4 vs. 0-1	1.28 (0.84-1.96)	0.255
APL included	t-AML *vs. de novo*	0.99 (0.62-1.57)	0.950
	Age	1.05 (1.04-1.06)	<0.001
	ECOG PS 2-4 *vs.* 0-1	1.40 (1.00-1.94)	0.048
APL only	t-AML *vs. de novo*	0.89 (0.40-2.00)	0.777
	Age	1.06 (1.03-1.08)	<0.001
	ECOG PS 2-4 *vs. 0-1*	2.24 (1.27-3.98)	0.006
Intermediate risk	t-AML *vs. de novo*	1.53 (1.25-1.87)	<0.001
	Age	1.04 (1.03-1.05)	<0.001
	ECOG PS 2-4 *vs.* 0-1	1.55 (1.34-1.79)	<0.001
Adverse risk	t-AML *vs. de novo*	1.59 (1.31-1.93)	<0.001
	Age	1.03 (1.02-1.04)	<0.001
	ECOG PS 2-4 *vs.* 0-1	1.56 (1.31-1.86)	<0.001

AML: acute myeloid leukemia; t-AML: therapy-related AML; APL: acute promyelocytic leukemia; OS: overall survival; HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

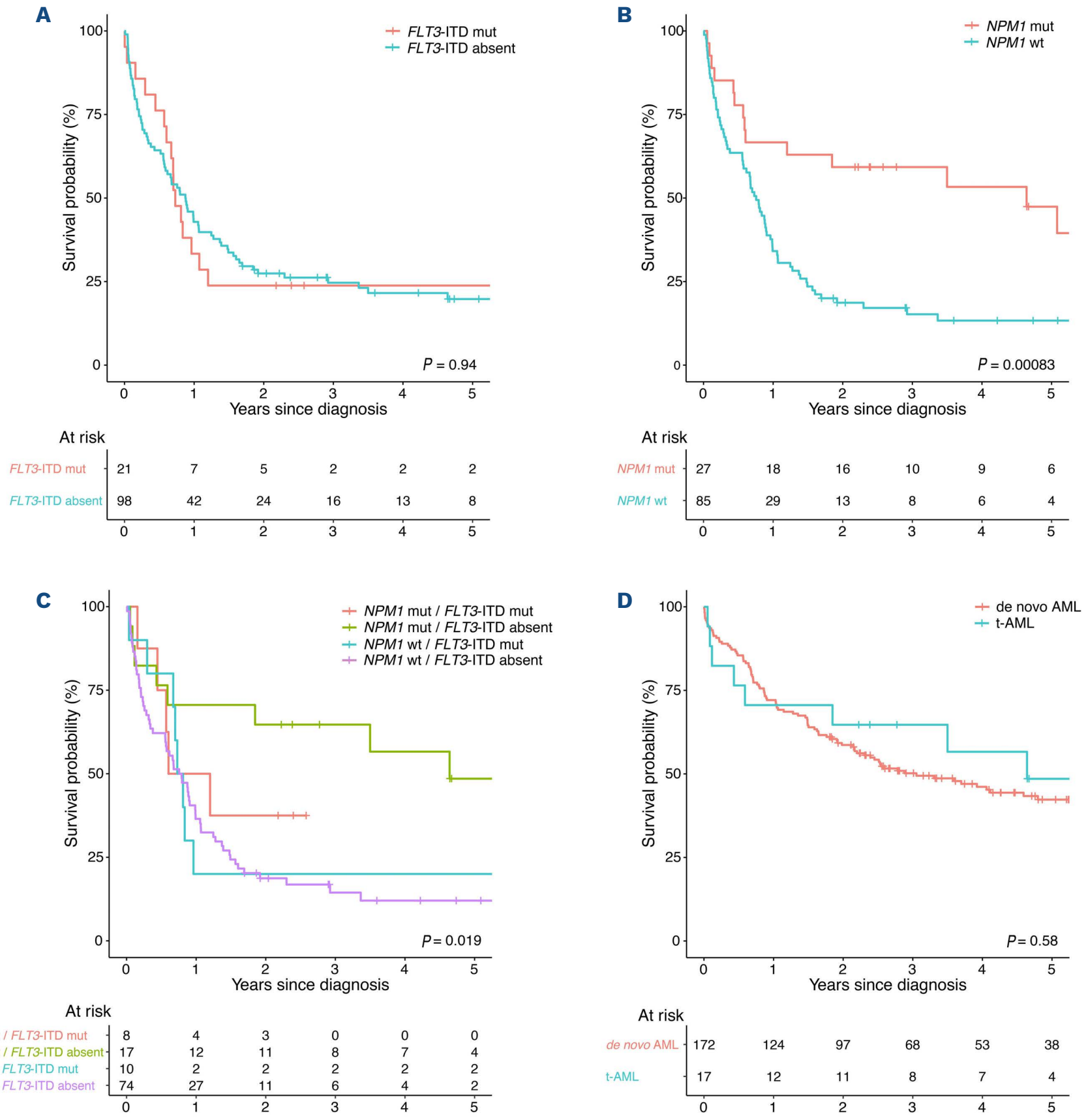


Figure 4. Survival in patients with therapy-related acute myeloid leukemia based on *NPM1* and *FLT3*-ITD status. Overall survival by (A) *FLT3*-ITD status, (B) *NPM1* mutational status and (C) *FLT3*-ITD/*NPM1* status in therapy-related acute myeloid leukemia (t-AML). (D) Comparison of overall survival between t-AML and *de novo* acute myeloid leukemia (AML) in patients with $NPM1^{mut}$/*FLT3*-ITD^{absent}.

survival differences in intermediate- and adverse-risk patients but a significant difference in the favorable-risk group.[29] However, their study was considerably smaller with 93 t-AML patients in total, making the numbers of patients in each cytogenetic risk group very small. Aldoss and Pullarkat have reviewed whether the outcome of patients with favorable-risk t-AML is comparable to that of those with favorable risk *de novo* AML.[31] The concluded that a therapy-related disease does not affect survival in APL but that it negatively affects outcome in core-binding factor AML, although not to a degree that should change transplantation indications in therapy-related core-binding factor leukemia. Our data support the approach that indications for allogeneic transplantation should remain the same in t-AML as *de novo* AML in patients with favorable-risk cytogenetics.

Mutational screening of *NPM1* and *FLT3*-ITD is part of clinical routine as well as ELN recommendations for prognostic

classification[32] and for the first time, we could study the role of t-AML in these mutational subcategories of AML. In our study, the presence of *FLT3*-ITD did not have a negative impact on survival in t-AML patients, while patients with *NPM1*^{mut} had a significantly better survival compared to those with *NPM1*^{wt} t-AML. The lack of impact of *FLT3*-ITD on survival may be due to the different cytogenetic pattern in t-AML, in which the prognostic role of *FLT3*-ITD can be dependent on the concomitant cytogenetic aberrations.[33] Also, all *FLT3*-ITD mutations, regardless of allelic ratio were included, which may impaired the prognostic power of our analysis. As in *de novo* AML, the survival of patients with *NPM1*^{mut}/*FLT3*^{wt} was better than that of patients with any other combination of these mutations.[34,35] Importantly, survival of t-AML patients with *NPM1*^{mut}/*FLT3*^{wt}, defined as favorable risk in ELN, did not differ significantly from that of *NPM1*^{mut}/*FLT3*^{wt} *de novo* patients in a multivariable analysis. This suggests that, similarly to cytogenetically favorable-risk AML, t-AML patients with *NPM1*^{mut}/*FLT3*^{wt} could be approached with the same treatment strategy as used for *de novo NPM1*^{mut}/*FLT3*^{wt} AML patients.

The reason for the worse outcome of intermediate- and poor-risk patients with t-AML, compared to their *de novo* counterparts, also when adjusting for other factors such as cytogenetics, age and performance status, is likely multifactorial. A higher frequency of unfavorable mutations and/or an enrichment of mutations originating from clonal hematopoiesis in patients with t-AML may contribute.[9,13,36] As data in this study emerge from the clinical routine, which did not include mutational screening until very late during the study period, mutational data are lacking in this study. Therefore, there is a need for future studies that elucidate the role of t-AML in the setting of full mutation information. Standard induction treatment for AML remained mainly unchanged during the study period. More recently, new therapeutic options have become available, and these could potentially change the course of the disease in the future. For instance, prolonged survival in AML, including t-AML, has been seen among patients treated with CPX351.[37] A broader use of hypomethylating agents alone or in combination with antibodies or novel inhibitors targeting *FLT3*, *IDH1/2* and *BCL2* also has the potential to improve outcome in certain subtypes of t-AML.

In summary, this large population-based study reveals a significant increase in the incidence of t-AML over time, which points to the reality of an increasing likelihood of encounter patients with this malignancy in the clinical practice. Thus, we need more knowledge of, as well as better treatment approaches for, these patients. Given the poor survival in t-AML it is especially important to develop non-chemotherapeutic treatment approaches to malignant and inflammatory diseases, which should result in a decreased risk of t-AML. Our data support an approach in which the indication for HCT should be the same in patients with favorable-risk cytogenetics or *NPM1*^{mut}/*FLT3*^{wt} with respect to previous chemotherapy or radiation treatment. On the contrary, intermediate- and adverse-risk patients with t-AML have even poorer survival compared to their *de novo* counterparts and novel treatment approaches for these patients are highly warranted.

Disclosures

No conflicts of interest to disclose.

Contributions

CN and SL designed the study and gathered, assembled and classified all data. CN and SL performed all analyses and interpreted the data with contributions from FL, EH, HG and LM. CN and SL wrote the manuscript. All other authors contributed to the Swedish AML registry. All authors critically reviewed and approved the manuscript.

Funding

The study was supported by the Swedish Cancer Foundation, Swedish Research Council and Stockholm County Council.

Data-sharing statement

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy concerns and limitations from the ethical review board but are available from the corresponding author upon reasonable request.

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