haematologica
Journal of the Ferrata Storti Foundation

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Received: December 23, 2025.
Accepted: February 18, 2026.

Citation: David Baden; Nadine Wolgast; Leo Ruhnke; Klaus Metzeler; Thomas Beder; Alexander Pohlmann; Sophie Steinhäuser; Jacqueline Müller-Nordhorn; Alexander Katalinic; Maria Teresa Voso; Claudia D. Baldus and Lars Fransecky. Nationwide analysis of acute promyelocytic leukemia: incidence and patient outcomes in Germany.
Haematologica. 2026 Feb 26. doi: 10.3324/haematol.2025.300427 [Epub ahead of print]

Nationwide analysis of acute promyelocytic leukemia: incidence and patient outcomes in Germany

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Short title: Epidemiology of acute promyelocytic leukemia

Key Words: Acute promyelocytic leukemia, APL, Epidemiology, PML::RARA, C92.4

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Funding: David Baden is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – project number 413490537 within the Kiel Clinician Scientist Program in Evolutionary Medicine (CSEM).

Acknowledgement: We thank the staff of all 16 state cancer registries (Baden-Württemberg, Bavaria, Berlin/Brandenburg, Bremen, Hamburg, Hesse, Mecklenburg-Western Pomerania, Lower Saxony (epidemiological and clinical registry), North Rhine-Westphalia, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, Schleswig–Holstein and Thuringia) as well as the staff of the Centre for Cancer Registry Data of the RKI the thorough processing and transmission of the data. The registries were not involved in the evaluation and interpretation and take no responsibility for the content of the manuscript.

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All authors interpreted the data, drafted, and reviewed the report, gave their final approval for publication, and agreed to be accountable for all aspects of the work.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement: The data sets analyzed in this study were provided by the German state cancer registries as well as the Center for Cancer Registry Data Germany and are available to researchers upon request.

Baden et al., Epidemiology of Acute Promyelocytic Leukemia

Data on incidence and survival of patients with acute promyelocytic leukemia (APL) in Europe are limited. In Germany (2016–2021), incidence was 0.127/100,000, with a 5-year overall survival rate of 75.2% that declined sharply with older age, while early mortality increased in older patients. These findings highlight the need for continued improvements of rapid diagnosis and management of patients in a largely curable disease.

Acute promyelocytic leukemia (APL) is a rare AML subtype defined by the t(15;17) translocation, which creates the PML::RARA fusion protein that blocks differentiation and apoptosis [1]. Clinically, patients often present with significant bleeding diathesis. Laboratory findings usually show anemia, thrombocytopenia, and abnormal coagulation tests, while leukocytosis is generally less frequent than in other AML subtypes, or absent. Because hemorrhagic diathesis increased the risk of fatal outcomes, rapid diagnosis by cytomorphology and genetic assays is crucial to facilitate immediate treatment initiation [2]. The current standard of care combines all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), leading to complete remission in over 90% of patients and high cure rates in clinical trials [2–4]. Only in high-risk APL defined by leukocyte counts >10,000/µl, ATO/ATRA treatment is preceded by a brief cytotoxic chemotherapy phase [2].

However, it is less-well known how these therapeutic advances of clinical trials translate into improved population-wide outcomes. Most population-based survival data predate ATO/ATRA therapy and may therefore not reflect current outcomes. Moreover, regional variations in APL incidence may affect diagnostic and treatment outcomes, while demographic, socioeconomic, and healthcare differences can limit the transferability of results across health care systems.

Patients newly diagnosed with APL between 2016 and 2021 identified by the International Classification of Diseases (ICD-10) Code C92.4 and morphology 9866/3 (ICD-O) were obtained from individual German federal cancer registries and the Center for Cancer Registry Data, where all cancer treatment facilities are legally required to report therapies and relevant patient events. These encompass diagnosis, confirmation by histology, cytology, or autopsy; initiation and completion of treatment, and outcome events, such as disease progression and death and are combined with regular reports from mortality registries. Age-standardized incidence rates were calculated using the European Standard Population 2013. Survival was analyzed using Kaplan–Meier estimates with log-rank tests, and multivariable models evaluated the effects of age and sex. Analyses were performed in R (v4.4.2); p-values <0.05 were considered significant. As only de-identified data were used, ethics committee approval was not required. The study complied with principles of good scientific practice and ethical guidelines and data usage was approved by the scientific boards of all German cancer registries.

First, we analyzed aggregated nationwide data from the Center for Cancer Registry Data in Germany. Between 2016 and 2021, 649 of 26,190 patients with AML (2.5%) received a diagnosis of APL, accounting for 108 cases of APL per year on average. Median age at diagnosis was 55.6 years (IQR: 41.8 - 69.4 years, range 3.7 - 93.3 years). Only 15 patients were under the age of 18 years. 327 (50.4%) patients were male, 322 patients were female, with no relevant difference in median age (56.8 vs 53.4 years, p=0.25).

The age-standardized incidence rate remained stable over the study period. We calculated a mean incidence of 0.127/100,000 (SD 0.009) inhabitants with equal distribution between males and females (ratio 1.09, Figure 1A). We noted increasing incidence rates with higher age when analyzing age-specific incidence rates (Figure 1B). Excluding the age group older than 85 years due to potential data missingness at random, a linear model with an R^2 of 0.94 demonstrated a strong linear relationship between APL incidence and age (Figure 1B). Accordingly, the highest incidence rates occurred in men aged >80 years old (0.294-0.319/100,000).

Using data directly obtained from the individual German federal cancer registries, survival data were available for 450 patients, with a median follow-up of 35.5 months (95%CI 33.4-38.8 months).

Overall survival (OS) of the entire cohort was 76.7% (95%CI 72.7–81.0%) at three years (3y-OS), and 75.2% (95%CI 70.9–79.7%) after five years (5y-OS). No significant survival difference between men and women was observed, with a 3y-OS of 75.1% (95%CI: 69.6–81.2%) for male patients and 78.5% (95%CI 72.9–84.6%) for female patients and a 5y-OS of 74.0% (95%CI 68.1–80.4%) for male patients and 76.5% (95%CI 70.4–83.1%) for female patients, respectively (p=0.48). Survival differed markedly by age: 5-year OS was highest in patients 0–59 years (87.9%), lower in those aged 60–74 years (70.8%), and worst in patients older than 75 years (25.7%, p<0.001, Figure 2, Supplement Table 1).

We analyzed outcomes with respect to treatment type. Of 450 patients, 232 (51.5%) were treated with ATO/ATRA alone, while 86 (19.1%) patients underwent intensified therapy with additional chemotherapy alongside ATO and/or ATRA. Nine patients with APL (2.0%) received an allogenic stem cell transplant, while no autologous stem cell transplant was reported. In 48 (10.7%) patients, only intensive therapy was documented without ATO or ATRA. Treatment details were missing for 84 patients (18.6%, Figure 3A).

Overall survival was most favorable in patients receiving ATO/ATRA, with a 3y-OS of 87.3% (95%CI 83.0–91.9%) (Figure 3B, Supplement Table 1). Patients receiving chemotherapy in addition to ATO and/or ATRA had a slightly less favorable 3y-OS of 77.4% (95%CI 68.6–87.3%). When intensive treatment without ATO/ATRA was administered, 3y-OS was 49.2% (95%CI 36.2–66.9%). These differences were consistent across all age groups (Supplement Figure 1). Age and treatment, but not sex, were independently associated with survival: Each year increased death risk by 5% (HR 1.05, 95%CI 1.04–1.07; p<0.001), and compared with ATO/ATRA, hazards were higher for ATO/ATRA with intensive

therapy, intensive treatment only, and unknown treatment (HRs 1.87, 4.23, 2.88; all p≤0.038). Sex showed no association with survival (HR 0.87; p=0.86).

Early mortality, defined as death within 60 days after diagnosis, was observed in 14.4 % (95%CI 11.1–17.6%) of patients in the entire cohort. Men and women were equally affected [16.2% (95%CI 11.4–20.8%) vs 12.5% (95%CI 8.0–16.8%, p=0.26)]. Early mortality rates increased with age, from 7.9% (95%CI 4.7–11%) in patients younger than 60 years, to 18.6% (95%CI 11.1–25.4%) in those aged 60-74 years and 37.3% (95%CI 23.7–48.5%) in patients older than 75 years (Supplement Figure 2). Early mortality was highest in patients receiving intensive chemotherapy (29.2%; 95%CI 15.1–40.9%) and lowest in those treated with ATO/ATRA (7.8%; 95%CI 4.3–11.1%).

This population-based analysis of 649 patients with APL provides a comprehensive overview of APL incidence and outcomes in Germany between 2016 and 2021.

With a stable incidence of 0.127 per 100,000, Germany shows an intermediate APL incidence internationally, comparable to Europe and the U.S. and lower than in parts of Asia. The unchanged rates suggest that no adjustments in healthcare infrastructure or personnel are needed based on incidence trends alone. Across 24 European countries, the mean APL incidence was 0.1 per 100,000, ranging nationally from 0.011 to 0.257 per 100,000, with generally higher rates in Southern than Northern Europe. [5]. Incidence rates at the upper end of this spectrum have also been described in Central and South America and China, where APL represents up to 19% of all AML cases [6,7]. In the United States, reported APL incidence ranges from 0.27 to 0.32 per 100,000, whereas Sweden documented an incidence of 0.15 per 100,000 in 2011 [8–12].

Introduction of treatment with ATO/ATRA improved overall survival in APL substantially, regardless of patient age, although survival rates still show significant age-dependent differences [13]. While we observed high 3-year OS of 87.3% in patients aged 0-59 years treated with ATO/ATRA, the 2-year overall survival in the pivotal study of Lo-Coco et al. of 99% exceeded our real-world results[3]. Despite a younger median age of 44.6 years compared with 55.6 years in the German Cancer Registry cohort, there remains substantial potential and need to further improve survival in this potentially curable disease.

The lower overall survival could be attributed to a higher early death rate especially in elderly patients, as we found 7.9% early death rates for patients younger than 60 years and a staggering 37.3% in patients older than 75 years. This is in line with US-based data reporting in-hospital death rates of 22.2% for patients >60 years compared to 6.4% for those <60 years after a median length of stay in hospital of 31 days [11]. We speculate that higher comorbidity and impaired organ function in elderly APL patients increase the risk of early complications and severe therapy-related adverse events. Some

early deaths likely involve post-mortem APL diagnoses, indicating that delayed diagnosis may contribute to these fatalities

Despite the inherent limitations of large database studies, our results indicate that both clinical expertise and robust care pathways, ensuring quick diagnosis and initiation of ATO/ATRA therapy, are likely key determinants of the high survival rates among patients with APL [14]. As treatment shifts toward oral regimens, the risks of life-threatening complications persist. We recommend connecting specialized primary care centers with secondary and tertiary providers, using telemedicine and other collaborative approaches to enable rapid testing, timely blood product use, and optimal management of differentiation syndrome.

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Figure Legend

Figure 1: Age-standardized and age-specific incidence rates of APL in Germany.
(A) Age-standardized incidence rates per 100,000.
(B) Age-specific incidence rates per 100,000.
Black lines represent the total population, while blue and red lines indicate male and female rates, respectively.

Figure 2: Overall survival by age group in patients with APL.
Five-year overall survival was 87.9% for patients ≤59 years, 70.8% for patients 60–74 years, and 25.7% for patients ≥75 years.

Figure 3: Treatment distribution and therapy-related survival in patients with APL.
(A) Distribution of therapy types by age and sex among 450 patients (ATO/ATRA: n = 232, ATO/ATRA + intensive treatment: n = 86, intensive treatment: n = 48, unknown: n = 84).
(B) Overall survival stratified by therapy type across age groups, favoring treatment with ATO/ATRA.
Abbreviations: *ATO: arsenic trioxide; ATRA: all-trans retinoic acid.*

Figure 1

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Fig 1A: Age-standardized incidence rate of APL

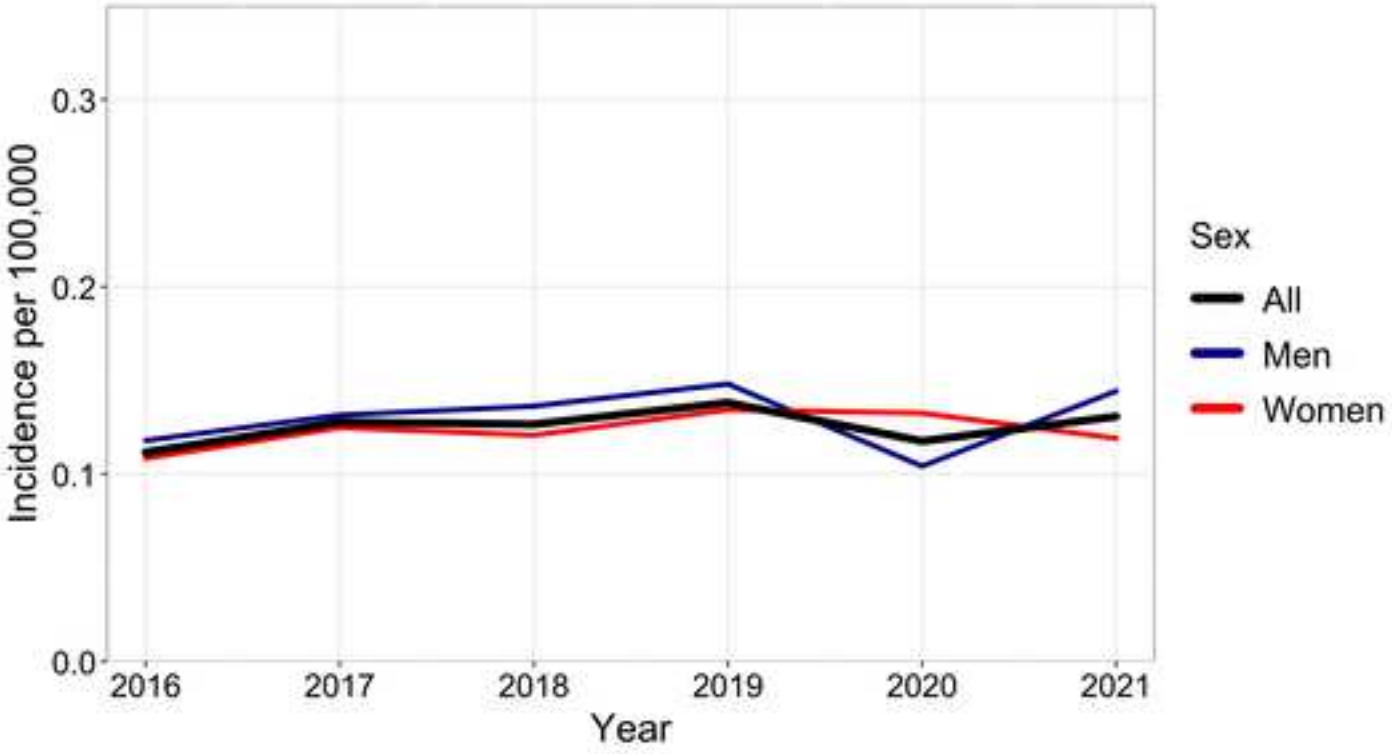


Fig 1B: Age-specific incidence rate of APL

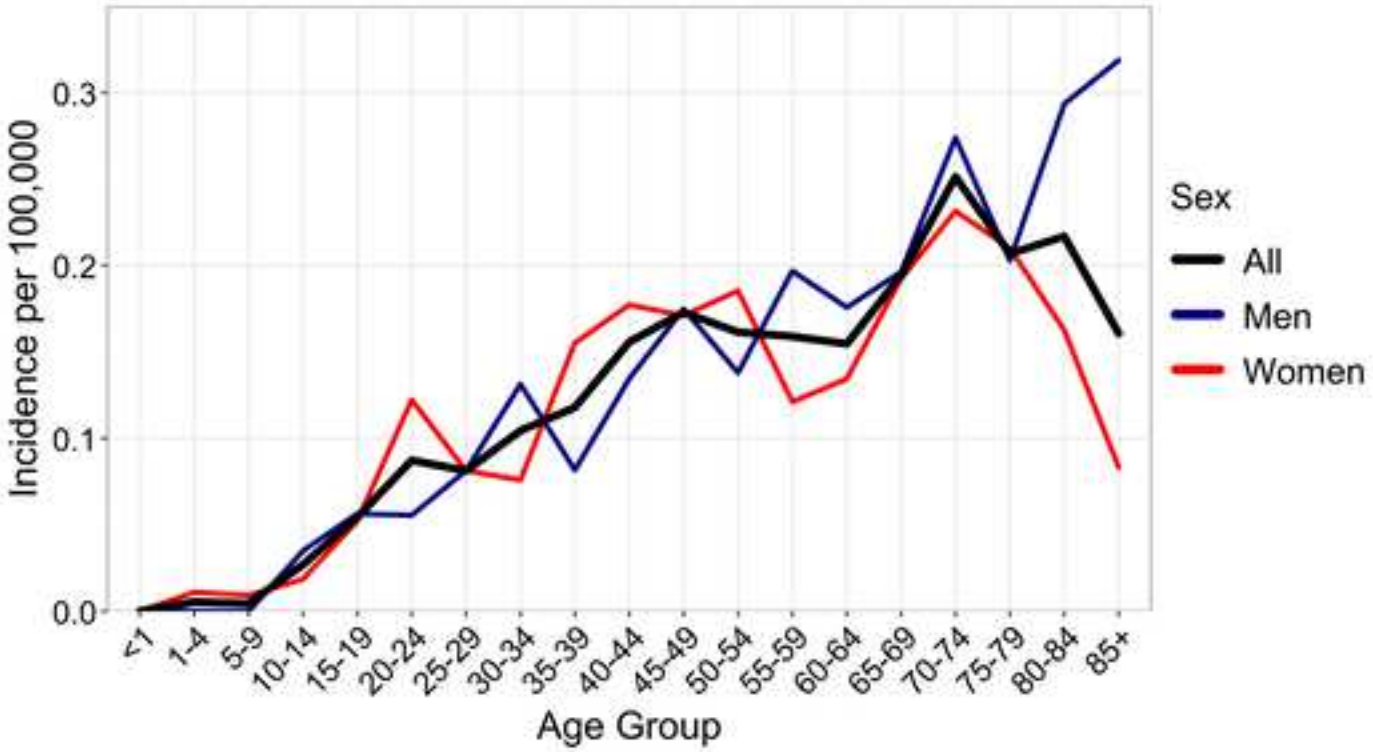
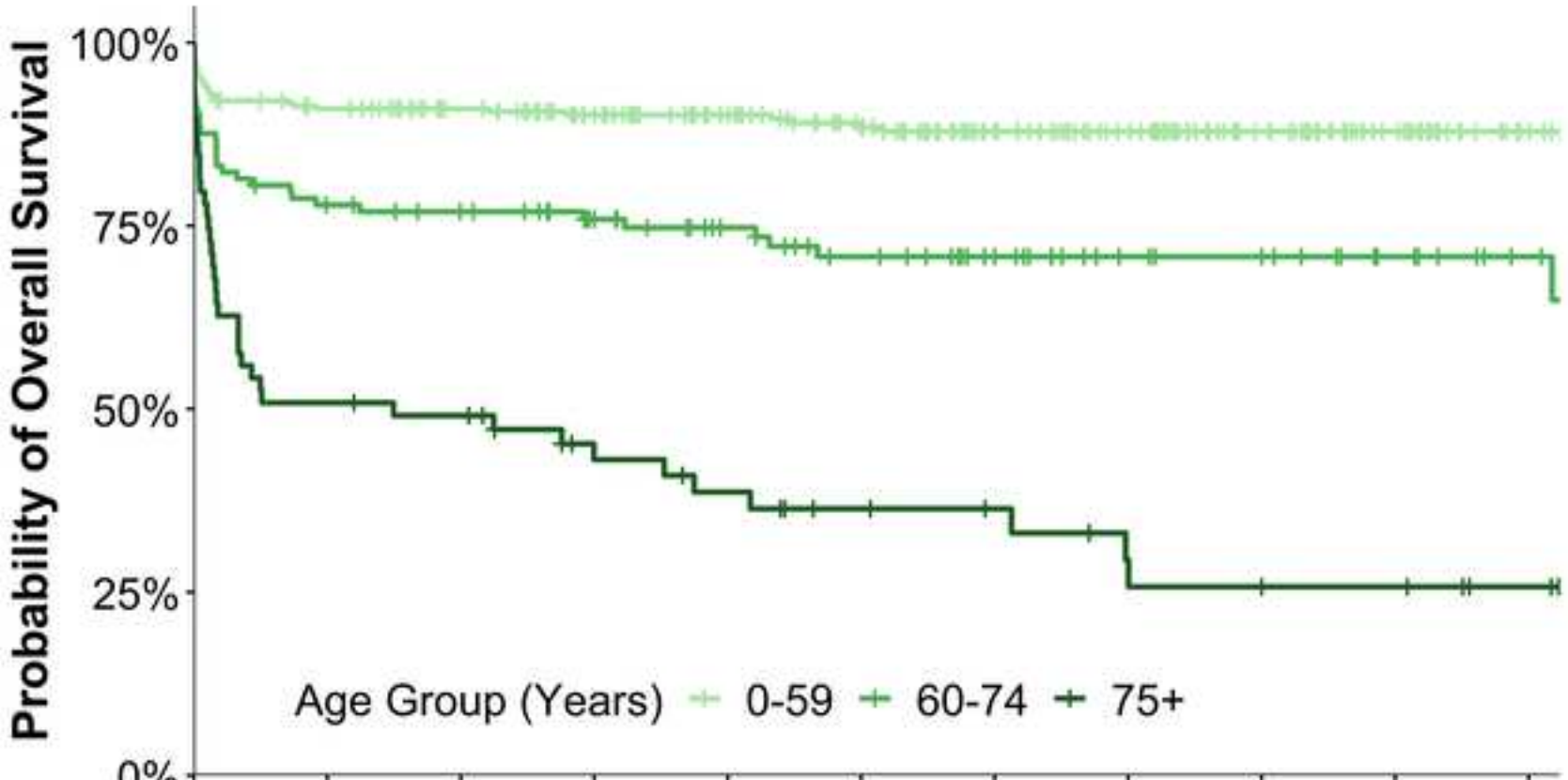


Figure 2

Fig 2: Overall survival of APL patients by age group



Number at risk

0-59	278	246	225	200	175	149	120	98	68	45	22
60-74	113	86	81	70	59	49	40	28	26	19	13
75+	59	30	28	20	17	13	11	8	7	6	3

Fig 3A: Distribution of therapy types by age group and sex

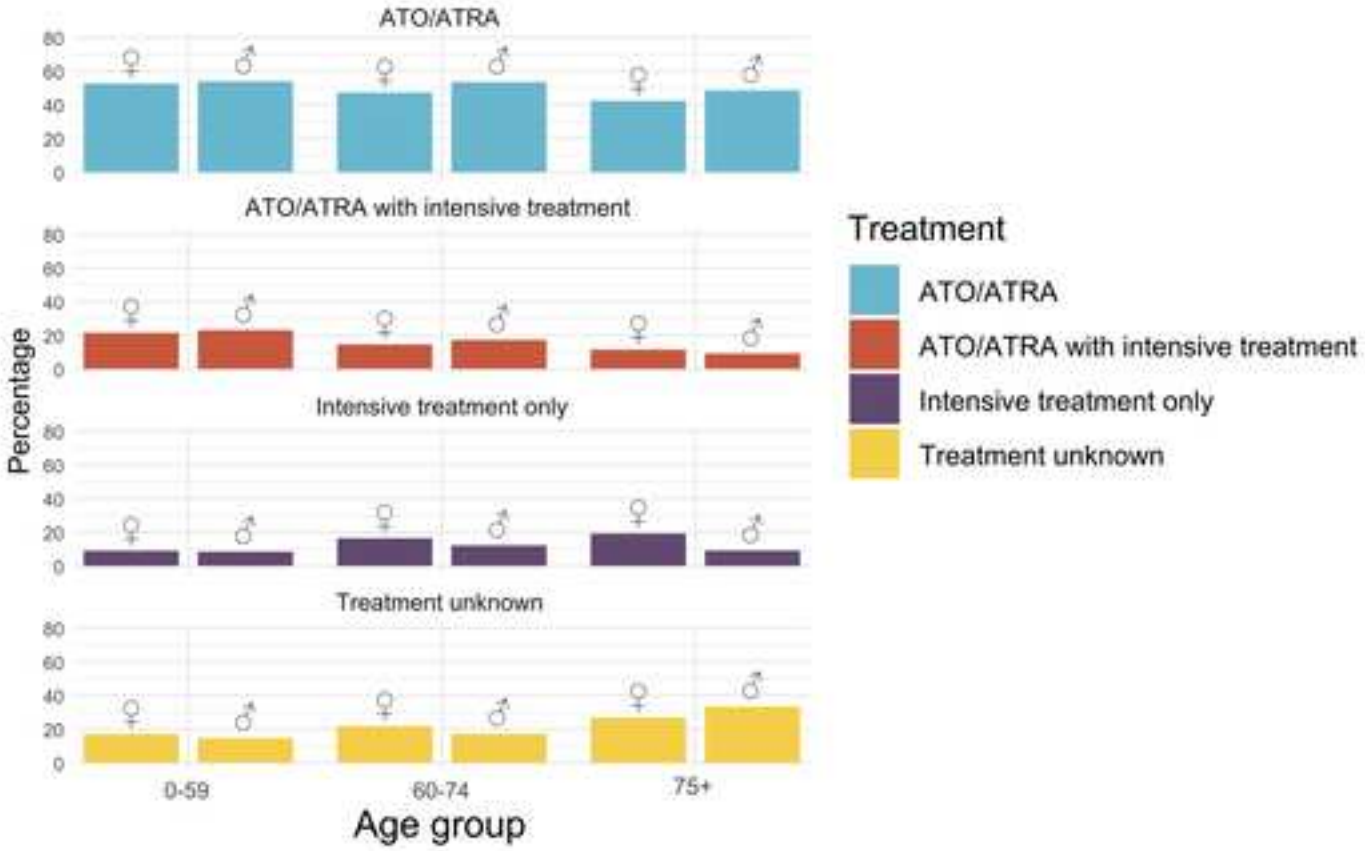
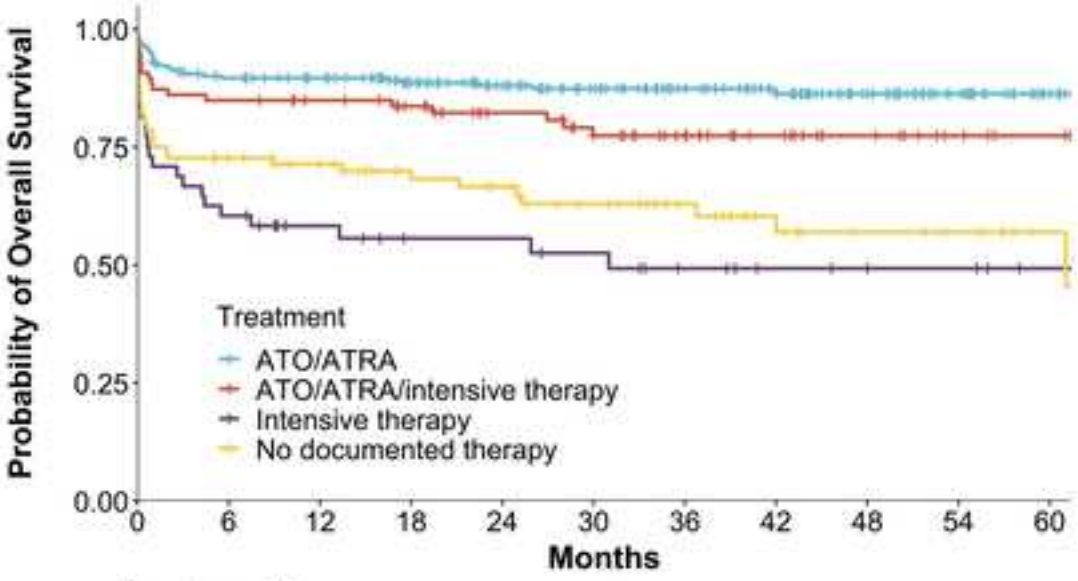


Fig 3B: Overall survival in APL by therapy type



Number at risk

ATO/ATRA	232	202	192	168	142	119	97	78	58	37	17
ATO/ATRA/intensive therapy	86	73	69	63	53	45	38	29	22	15	12
Intensive therapy	48	29	22	18	18	16	12	9	8	7	4
No documented therapy	84	58	51	41	38	31	24	18	13	11	5

Nationwide analysis of acute promyelocytic leukemia: Incidence and patient outcomes in Germany - Supplement

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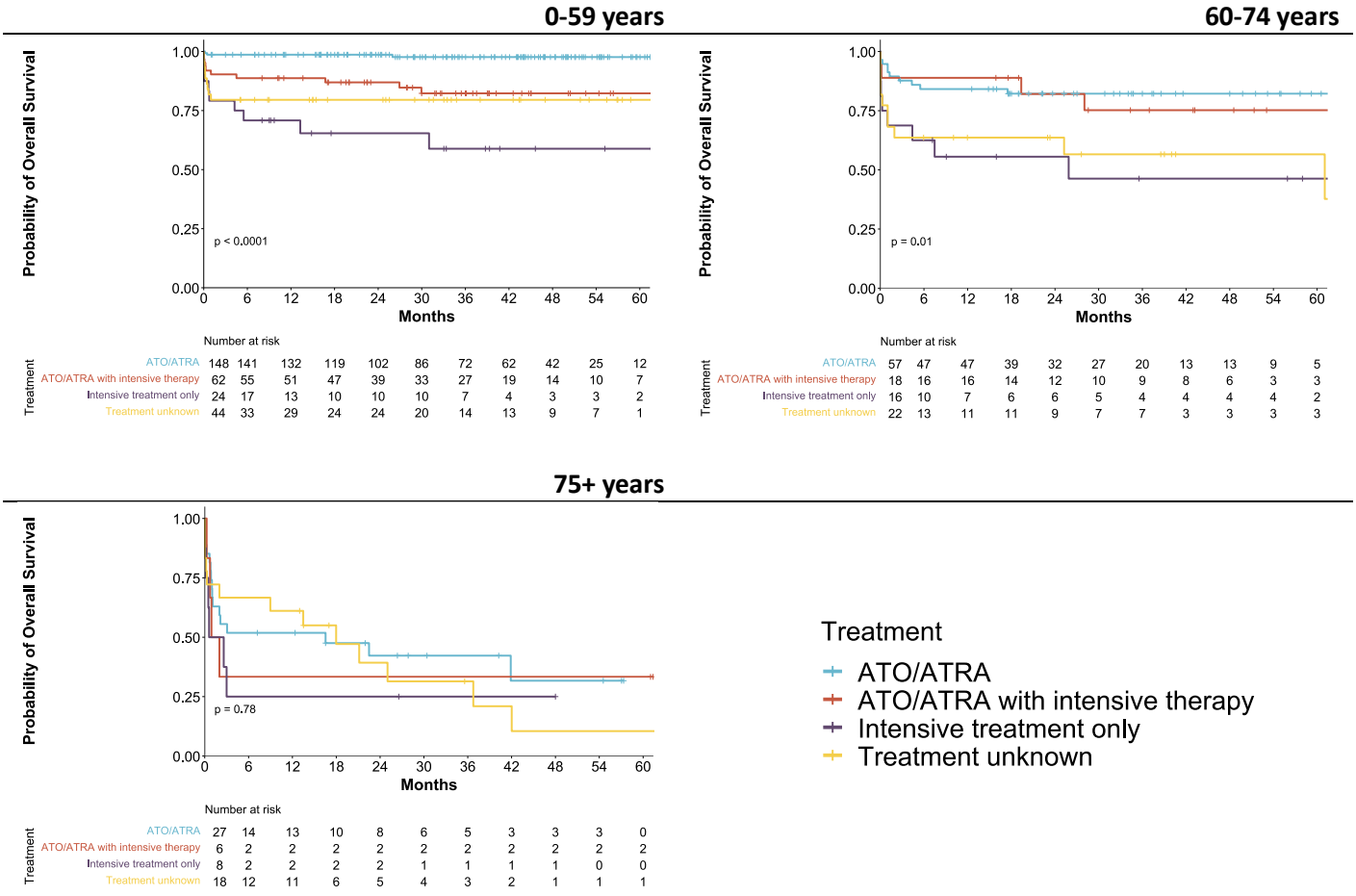
Supplement Table 1: Three- and five-year survival rates and 60-day mortality rate by age group and treatment

	OS 3 year (%, 95% CI)	OS 5 years (%, 95% CI)	60-day mortality rate (%, 95% CI)
Age group			
≤59	87.9 (83.9–92.0)	87.9 (83.9–92.0)	7.9 (4.7–11.0)
60-74	70.8 (62.5–80.2)	70.8 (62.5–80.2)	18.6 (11.1–25.4)
75+	36.4 (25.5–51.9)	25.7 (15.1–43.8)	37.3 (23.7–48.5)
Treatment			
ATO/ATRA	87.3 (83.0–91.9)	86.2 (81.5–91.2)	7.8 (4.3–11.1)
ATO/ATRA/IT	77.4 (68.6–87.3)	77.4 (68.6–87.3)	12.8 (5.4–19.6)
IT	49.2 (36.2–66.9)	49.2 (36.2–66.9)	29.2 (15.1–40.9)
Unknown	62.9 (52.8–75.0)	56.9 (45.5–71.3)	26.2 (16.2–35.0)

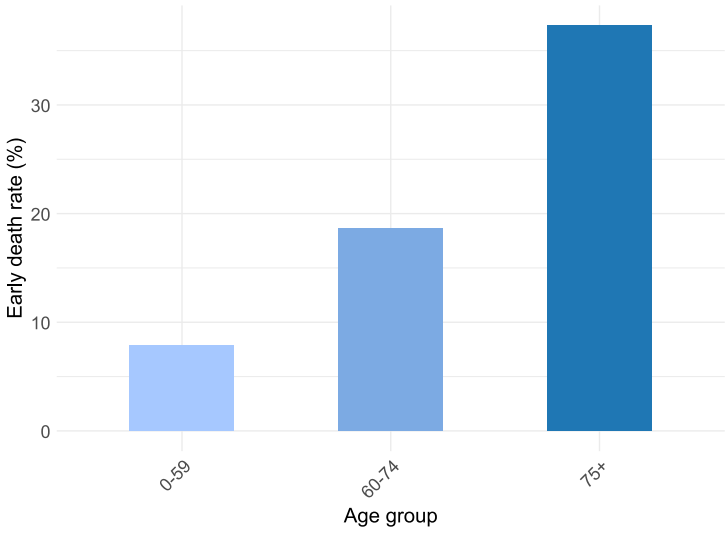
Supplement Table 1: Overall Survival after 3 and 5 years and early mortality rate after 60 days of patients diagnosed with APL between 2016-2021 in Germany stratified by age group and treatment. *Abbreviations: ATO: arsenic trioxide, ATRA: all-trans retinoic acid, IT: intensive treatment and/or additional chemotherapy*

Supplement Figure 1: Overall survival of APL-patients by therapy type and age group



Supplement Figure 1: Overall survival of patients with APL, stratified by treatment and age groups. *Abbreviations: ATO: arsenic trioxide, ATRA: all-trans retinoic acid*

Supplement Figure 2: Early death rate by age group



Supplement Figure 2: Early death rate by age group after 60 days. Early mortality increased from 7.9% (95% CI 4.7–11%) in patients under 60 years to 18.6% (95% CI 11.1–25.4%) at ages 60–74 and 37.3% (95% CI 23.7–48.5%) in those 75 years and older.