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

Acute promyelocytic leukemia (APL) is a rare acute myeloid leukemia (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 is 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 >10x10^9/L, 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,

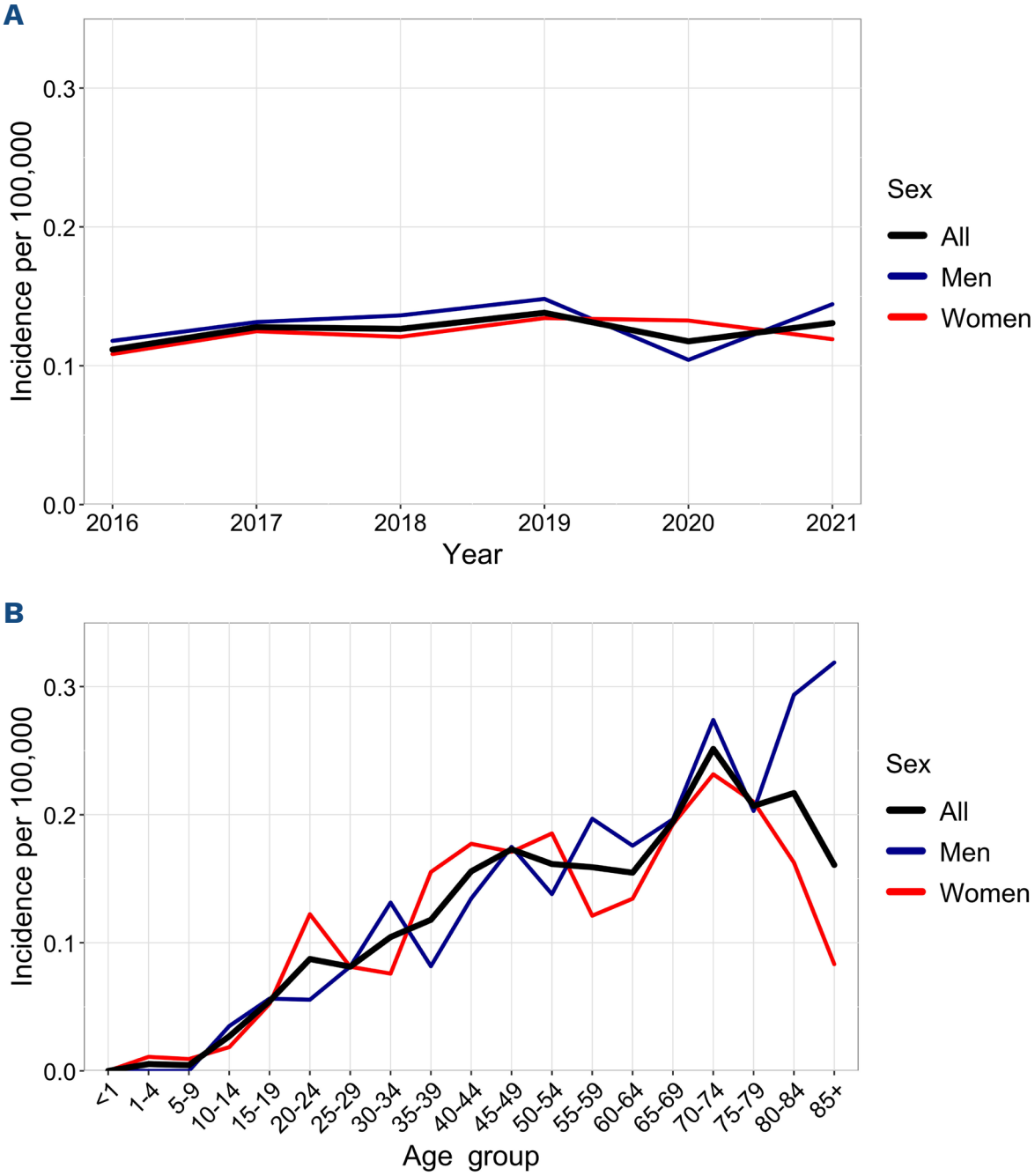

Figure 1. Age-standardized and age-specific incidence rates of acute promyelocytic leukemia in Germany. (A) Age-standardized incidence rates per 100,000. (B) Age-specific incidence rates per 100,000. Black lines represent the total population, while blue and red lines indicate male and female rates,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

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 (interquartile range [IQR]: 41.8-69.4 years, range 3.7-93.3 years). Only 15 patients were under the age of 18 years. A total of 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 (standard deviation [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 missing 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 (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 (3-year OS), and 75.2% (95% CI: 70.9-79.7%) after five years (5-year OS). No significant survival difference between men and women was observed, with a 3-year 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, a 5-year 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 aged 0-59 years (87.9%), lower in those aged 60-74 years (70.8%), and the worst in patients older than 75 years (25.7%, *P*<0.001) (Figure 2, *Online Supplementary Table S1*).

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 allogeneic 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 3-year OS of 87.3% (95% CI: 83.0-91.9%) (Figure 3B, *Online Supplementary Table S1*). Patients receiving chemotherapy in addition to ATO and/or ATRA had a slight-

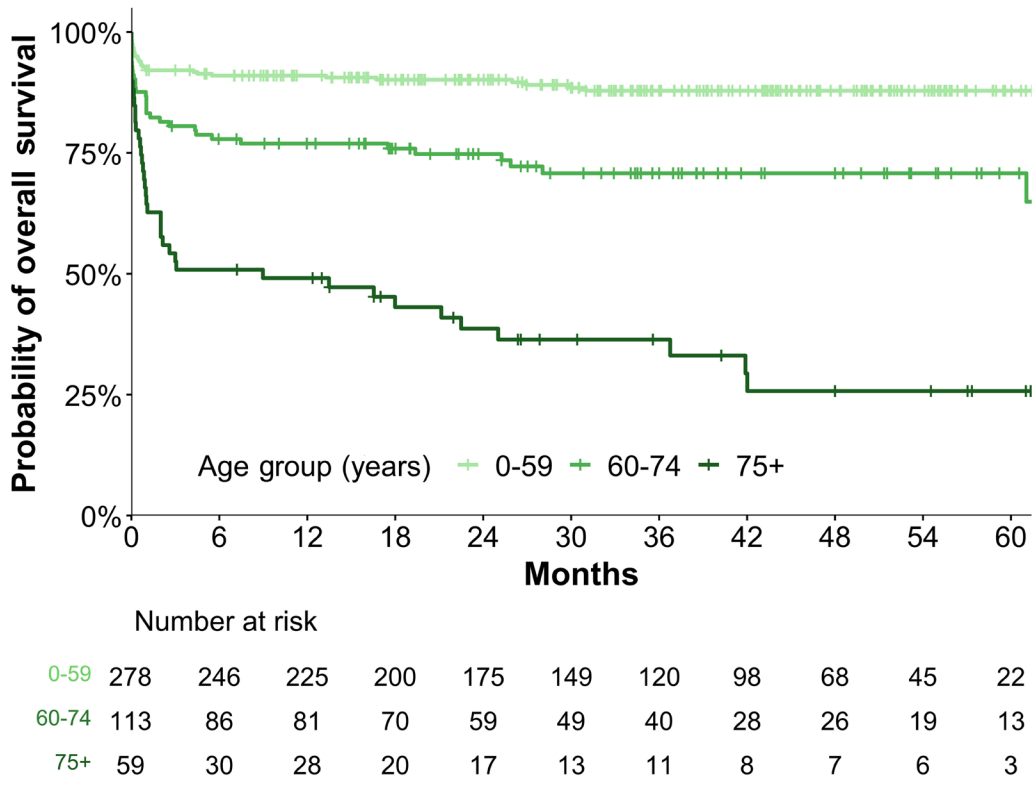

Figure 2. Overall survival by age group in patients with acute promyelocytic leukemia. 5-year overall survival was 87.9% for patients ≤59 years, 70.8% for patients 60-74 years, and 25.7% for patients ≥75 years.

ly less favorable 3-year OS of 77.4% (95% CI: 68.6-87.3%). When intensive treatment without ATO/ATRA was administered, 3-year OS was 49.2% (95% CI: 36.2-66.9%). These differences were consistent across all age groups (*Online Supplementary Figure S1*). 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, hazard ratios were higher for ATO/ATRA with intensive therapy, intensive treatment only, and unknown treatment (HR 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

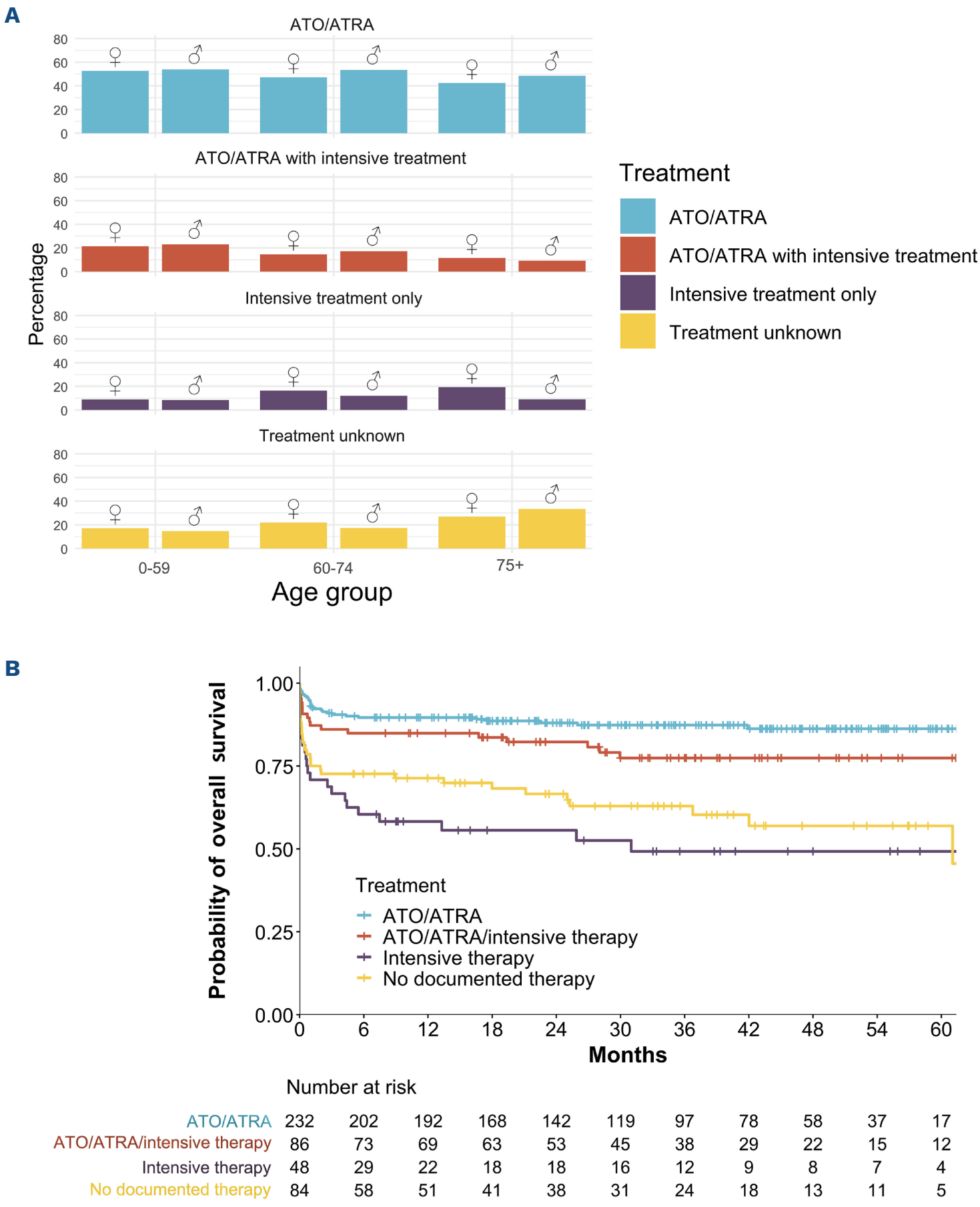

Figure 3. Treatment distribution and therapy-related survival in patients with acute promyelocytic leukemia. (A) Distribution of therapy types by age and sex among 450 patients. ATO/ATRA: N=232, ATO/ATRA + intensive treatment: N=86, intensive treatment: N=48, unknown: N=84. (B) Overall survival stratified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

(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 under 60 years of age, 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 over 75 years of age (*Online Supplementary Figure S2*). 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 US, 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 OS 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 OS 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 considerable potential and need to further improve survival in this largely curable disease.

The lower OS could be attributed to a higher early death rate especially in elderly patients, as we found 7.9% early death rates for patients under 60 years of age and a staggering 37.3% in patients over 75 years of age. This is in line with US-based data reporting in-hospital death rates of 22.2% for patients aged >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, and using telemedicine and other collaborative approaches to enable rapid testing, timely blood product use, and optimal management of differentiation syndrome.

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Disclosures

No conflicts of interest to disclose.

Contributions

DB is responsible for study concept, data curation, formal analysis, investigation, project administration, visualization, wrote the original draft, and wrote, reviewed and edited the manuscript; CDB is responsible for study concept, project administration and study supervision, and wrote, reviewed and edited the manuscript; NW is responsible for data curation, formal analysis, investigation, and wrote, reviewed and edited the manuscript; LF is responsible for data curation, formal analysis, investigation, project administration,

study supervision, visualization, wrote the original draft, and wrote, reviewed and edited the manuscript; TB is responsible for formal analysis, and wrote, reviewed and edited the manuscript; LR is responsible for investigation, and wrote, reviewed and edited the manuscript; KM, AP, SS, JM-N, AK and MTV wrote, reviewed and edited the manuscript. 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.

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Data-sharing 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.

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