The national burden of Leukemia in Italy from 1990 to 2023: results from the Global Burden of Disease Study 2023

GBD 2023 Italian Leukemia Collaborators[u]

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Summary

Background Following the Global Burden of Disease (GBD) Study 2023 estimates, leukemias globally accounted for 573,000 new cases and 341,000 deaths in 2023. This study investigated the global burden of leukemia at level 3 (leukemia) and 4 (acute lymphoid leukemia-ALL, chronic lymphoid leukemia-CLL, acute myeloid leukemia-AML, chronic myeloid leukemia-CML and other leukemia) and its temporal trends from 1990 to 2023, at Italian national level.

Methods We used the GBD 2023 estimates to describe the leukemia age-standardized incidence (ASIR), mortality (ASMR), and disability-adjusted life years (ASDR) rates in Italy, the related 1990–2023 crude all-ages and age-standardized average annual rates of changes (ARC), as well the age-standardized mortality-to-incidence ratio (ASMIR). Finally, national estimates were compared to the GBD Global and High-middle Socio-Demographic Index (SDI) countries ones.

Findings In Italy in 2023, the GBD 2023 estimated 15,600 leukemia new cases, 7100 deaths and 136,700 DALYs. The 1990–2023 ARC for ASIR significantly improved only for rare leukemias (–0.46 95% UI: –0.60 to –0.26), while no significant changes were found for ALL, CLL, AML, CML. The ARC for ASMR and ASDR significantly improved for all leukemia subtypes, except for AML. The ARC for ASMR was –0.50 (–0.60 to –0.38) for ALL, –0.39 (–0.50 to –0.29) for CLL, 0.26 (0.07–0.49) for AML, –0.75 (–0.81 to –0.68) for CML and –0.49 (–0.59 to –0.30) for other leukemias. Similarly, the ARC for ASDR was –0.57 (–0.66 to –0.47) for ALL, –0.48 (–0.57 to –0.37) for CLL, –0.06 (–0.22 to 0.14) for AML, –0.80 (–0.85 to –0.74) for CML, and –0.57 (–0.66 to –0.41) for other leukemias. These findings translated into a similar pattern for the MIR.

Interpretation The global burden of leukemia in Italy is significantly reducing in terms of mortality and DALYs, especially for CML and ALL; on the other hand, AML-related measures greatly worsened over time. The Italian national ARC for incidence, mortality and DALYs showed comparable trends over time to the GBD Global and High-middle SDI countries ones, with specific differences.

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Keywords: Global Burden of Disease Study 2021; Leukemia; Incidence; Prevalence; Mortality; Disability-Adjusted Life Years (DALYs); Age-standardized incidence rate (ASIR); Age-standardized prevalence rate (ASPR); Age-standardized mortality rate (ASMR); Age-standardized DALY rate (ASDALYS); Age-standardized mortality-to-incidence ratio (ASMIR)

Introduction

Leukemia is a family of blood malignant neoplasms, early reported at the beginning of the 19th century: the German pathologist Rudolf Virchow published the first complete description of leukemia in 1856,[1] while his colleague Wilhelm Ebstein introduced the concept of acute leukemia in 1889.[2] The 2030 Agenda for Sustainable Development, adopted by the United Nations in 2015, defined 17 world Sustainable Development Goals (SDGs)[3]: Goal 3 (Good health and well-being)

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Research in context

Evidence before this study

Although the Global Burden of Disease Study (GBD) has published extensive analyses on cancer burden at the global and national levels, no previous GBD study has specifically and comprehensively focused on leukemia in Italy. However, subnational estimates of leukemia burden are essential for guiding local health policy and resource allocation. While national data sources such as AIRTUM, ISTAT, and AIOM offer valuable epidemiological insights, they remain fragmented and regionally heterogeneous. AIRTUM provides cancer incidence data at the registry level, but coverage is incomplete and varies across regions. ISTAT reports mortality statistics by region and province but does not systematically disaggregate leukemia by subtype or provide disability-adjusted metrics over time. AIOM's annual reports largely summarize national-level trends and focus on other types of cancers. Therefore, these sources do not consistently deliver long-term, comprehensive, and subtype-specific estimates at the subnational level, limiting their usefulness for monitoring trends or guiding region-specific cancer control strategies.

Added value of this study

This study provides the first comprehensive assessment of the leukemia burden in Italy using GBD 2023 estimates. We present national- and subnational-level data on incidence, mortality, Disability-Adjusted Life Years (DALYs), and the mortality-to-incidence ratio (MIR) for leukemia and its five main subtypes—acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and other leukemias—over the period 1990–2023. Temporal trends were evaluated using age-standardized rates and average annual rates of change (ARC) and compared with estimates for the GBD Global and High-middle Socio-Demographic Index (SDI) country groups. Our findings show a substantial and consistent decline in leukemia-related mortality and DALYs across most subtypes, particularly for CML and ALL. In contrast, AML displayed a concerning increase in both incidence and mortality over time. Stratified analyses by sex and age further highlight disparities in leukemia burden and underscore the evolving impact of diagnostic and therapeutic innovations.

Implications of all the available evidence

Despite meaningful improvements in leukemia burden in Italy—especially for CML and ALL—AML remains a critical concern with increasing incidence and limited survival improvement. These trends highlight the need for targeted prevention strategies, early diagnosis, and improved therapeutic options. Our findings underscore the importance of continuous, granular surveillance of hematologic malignancies using robust and comparable sources. This approach is essential for informing national cancer control strategies and aligning with global targets in the context of the Sustainable Development Goals.

includes several targets for non-communicable diseases. Among them, the reduction of under-5 mortality to at least 25 per 1000 live births and the reduction by one third of premature mortality from non-communicable diseases, are closely relevant to the fight against the burden of leukemia.[4] The GLOBOCAN 2022 Study by the International Agency for Research on Cancer estimated for the year 2022, 486,800 leukemia incident cases and 305,000 deaths, ranking 13th among 36 cancers for incidence and 10th for mortality, and accounting for 2.4% of the new cancer cases and 3.1% of cancer deaths, respectively.[5] As for Cancer Statistics 2025 from the American Cancer Society, leukemia is expected to cause in 2025, 66,900 new cases and 23,500 deaths in the USA, with 67% of patients alive 5 years after the diagnosis in 2020; this figure represents a doubling of the 34% in 1977.[6]

The Global Burden of Diseases, Injuries and Risk Factors Study 2023 (GBD 2023) assessed the burden of diseases in 204 countries and globally estimated for the year 2023, 1,449,400 incident cases and 775,500 deaths due to onco-hematological cancers (adding leukemia, multiple myeloma and Hodgkin/Non-Hodgkin lymphomas): of them, leukemia accounted for 573,000 incident cases and 341,000 deaths.[7] Following a well-established classification, the GBD 2023 divided leukemia into four main subtypes: acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML), while the rarer subtypes were labeled as "other leukemia". The leukemia age-standardized incidence rate/100,000 population varied across the seven GBD Super Regions from 3.71 to 13.59 in 1990, and from 3.02 to 11.42 in 2023, the highest rates being associated with the High-Income Super Region.[7] In the same timeframe, the leukemia age-standardized incidence rate for Italy (17.72 and 14.17) was significantly higher than the Global (8.66 and 6.70) and the High-middle Socio-Demographic Index (SDI) countries (7.57 and 5.88) ones. The Italy's unique sociodemographic profile and healthcare disparities make it a critical case study for understanding leukemia tendencies, with insights that could inform both national and global strategies. These observations induced us to conduct a detailed analysis on our country: the current analysis explored the national burden of leukemia in Italy with GBD 2023 Study estimates, relative to incidence, mortality and Disability-Adjusted Life Years (DALYs), as well as their corresponding temporal trends from 1990 to 2023.

Additionally, the analysis will compare the burden of leukemia in Italy with global estimates and with those of high-middle SDI countries, the quintile to which Italy belongs.

Methods

Overview

The GBD 2023 updated the GBD 2021 estimates of morbidity and mortality across geographical regions, time, age and sex, contributing to a global assessment of the disease burden. The GBD 2023 analysed 375 diseases and injuries, 292 causes of death and 88 environmental and occupational, behavioural, and metabolic risks. Italy ranks as the fifth-largest data contributor to the GBD 2023 Study, providing 1658 sources, including vital registration systems, national surveys, disease registries, and administrative datasets. Specifically for leukemia, 45 unique data sources—including disease registries and vital registration systems—and a total of 421,985 metadata records were used to inform the estimation process for Italy.

The methods for the generation of GBD 2023 estimates have been previously described[7]: they complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).[8] Additional details on the modeling strategies used for mortality and disability related to MM are available in the Supplementary File. Statistical analyses were performed by R version 4.5.0.[9] This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.[10]

GBD measures

The Italian national estimates for leukemia, including acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and other leukemia (i.e., eosinophilic leukemia, hairy cell leukemia, plasma cell leukemia and other rarer ones), were reported for 1990 and 2023. The leukemia burden has been described as incident cases, crude all-ages and age-standardized incidence rates (ASIR), death cases, crude all-ages and age-standardized mortality rates (ASMR), Disability-Adjusted Life Years (DALYs), crude all-ages and age-standardized DALYs rates (ASDR), and by their corresponding 1990–2023 crude all-ages and age-standardized annualized rate of change (ARC). DALYs were defined as the sum of the Years Lived with Disability (YLDs) and the Years of Life Lost (YLLs). ARC was calculated as the difference in the natural logarithm of the values at the start and end of the time interval divided by the number of years in the interval. Final estimates represent the median estimate across 500 draws, and 95% uncertainty intervals (UIs) are derived as the 2.5th and 97.5th percentile values across the draws. All rates have been reported per 100,000 person-years and the GBD world population age standard has been used for the estimation of all age-standardized rates. The above-described metrics have been reported both aggregated and disaggregated by sex and five age classes (<5/5–14/15–49/50–74 and 75+ years). The ASMR and ASDR have been also reported for all causes, only neoplasms and only leukemia. The leukemia-related survival has been approximated by the age-standardized mortality-to-incidence ratio (ASMIR) for 1990 and 2023.

Comparisons with the GBD 2023 global and high-middle SDI countries estimates

The ASIR, ASMR and ASDR, at the Italian national level, as well as their average ARC from 1990 to 2023, have been reported in comparison to the GBD 2023 Global estimates and the High-middle SDI countries. SDI is a composite indicator of development status, built as a geometric mean of 0–1 indices of total fertility rate for females under age 25, average years of education in ages 15 years and older, and lag-distributed income per capita. The GBD 2023 divided all countries into five SDI-dependent custom regions (grouped as quintiles, low/low-middle/middle/high-middle/high): Italy belongs to the high-middle SDI quintile.

GBD causes hierarchy and WHO-ICD codes for leukemia

In GBD 2023, the causes of health loss are aggregated in a four-level classification, at increasing specificity. For the current research, we focused on level 1 "Noncommunicable diseases" (B), level 2 "Neoplasms" (B.1), level 3 "Leukemia" (B.1.32) and level 4 "Acute lymphoid leukemia" (B.1.32.1), "Chronic lymphoid leukemia" (B.1.32.2), "Acute myeloid leukemia" (B.1.32.3), "Chronic myeloid leukemia" (B.1.32.4), and "other leukemia" (B.1.32.5). All the reported analyses have been performed at level 4. Version 10 of the WHO International Classification of Diseases (ICD) was used and the associated codes were: Leukemia C91–C95.9/ALL C91.0/CLL C91.1/AML C92.0, C92.3–C92.6, C93.0, C94.0, C94.2, C94.4–C94.5/CML C92.1/other leukemia C91.2–C91.9, C92.2, C92.7–C92.9, C93.1–C93.9, C94.1, C94.3, C94.6–C95.9.[11]

Data extraction and reporting

All the estimates were extracted from the Global Health Data Exchange tool (http://ghdx.healthdata.org/gbd-results-tool),[12] and the results have been presented for the years 1990 and 2023 as count estimates (incident cases, death cases and DALYs) and their corresponding average annual percentage changes from 1990 to 2023, as well the crude all-ages and age-standardized rates per 100,000 population (ASIR, ASMR and ASDR) and their corresponding ARC from 1990 to 2023. All data are shown with 95% uncertainty intervals (UIs); the differences in median percentage changes were considered significant if 95% UIs did not overlap.

Role of the funding source
The funders of this study had no role in study design, data collection, data analysis, data interpretation, or the writing of this report. The corresponding author had full access to all the data in the study and had the final responsibility to submit it for publication.

Results

The burden of leukemia in Italy: leukemia at level 3

Incident cases were 12,329 in 1990, and 15,586 in 2023. However, the ASIR was 17.72 (11.48–30.33) in 1990 and 14.17 (9.21–19.48) in 2023, with a non-significant ARC of –0.20 (–0.54 to 0.43) (Table 1). As for mortality, 5502 and 7100 persons died of leukemia, with a great improvement in ASMR from 6.82 (6.23–7.43) to 4.69 (4.09–5.19), and a significant ARC equal to –0.31 (–0.39 to –0.22). The age-standardized MIR showed a consequent improvement over time (from 38.5 to 33.1), with a larger recovery among males (Table 2). As for the DALYs estimates, the burden of leukemia at level 3 was associated with 156,663 and 136,708 DALYs, respectively. The ASDR significantly decreased from 234.08 (206.63–257.70) to 128.15 (114.59–142.58), with an ARC equal to –0.45 (–0.52 to –0.36). The burden of leukemia at level 3 (as to say, all forms of leukemia) has an aggregate-level epidemiological value; the four main subtypes and the rarer leukemias present very different clinical and pathological characteristics and need to be reported separately (Table 3, Figs. 1–3).

The burden of leukemia in Italy: leukemia at level 3, compared to GBD all causes and all neoplasms

Table 4 summarizes the variations over time for mortality and DALYs, following the GBD causes hierarchy. In 2023, the Italian national ASMR for all causes (level 1) was 389.37 (387.56–390.97) and the ARC for ASMR was equal to –0.40 (–0.40 to –0.39): these rates correspond to 672,400 estimated deaths cases at the country level. Of them, around 190,200 death cases were due to neoplasms (level 2): the ASMR for neoplasms was 121.51 (110.22–128.20) and the ARC for ASMR equal to –0.32 (–0.35 to –0.29). Of these, around 7100 death cases were due to all forms of leukemia, 3.7% of all neoplasms: the ASMR for leukemia was 4.69 (4.09–5.19), while the ARC significantly declined (–0.31; –0.39 to –0.22). Similarly, the ARC for ASDR was equal to –0.26 (–0.30 to –0.23), –0.37 (–0.39 to –0.35) and –0.45 (–0.52 to –0.36), being significant for "all causes", "all neoplasms" and "all forms of leukemia", respectively.

The burden of leukemia in Italy: leukemia at level 3, compared to GBD Global and High-middle SDI countries.

Table 5 shows the 1990–2023 estimates for leukemia at level 3, for ASIR, ASMR, ASYLD, ASYLL and ASDR and the corresponding ARC, compared to those estimated for GBD Global and High-middle SDI countries. In 2023, the Italian leukemia ASIR (14.17) was significantly higher than the Global (6.70) and the High-middle SDI countries ones (5.88); at the same time, no significant decline in the ARC for ASIR occurred in Italy (–0.20), globally (–0.23) and in High-middle SDI countries (–0.22). As for the leukemia-associated mortality, the ASMR for 2023 was equal to 4.69/3.95/3.53, with an overall significant improvement in the ARC for ASMR (–0.31/–0.34/–0.42). The ASDR for 2023 was comparable in the three areas (128.15/147.92/151.86), with a ubiquitous significant decrease in the ARC for ASDR (–0.45/–0.41/–0.49).

The burden of leukemia in Italy, disaggregated by age classes

Supplementary Tables S1–S6 show the rates of incidence, mortality and DALYs, disaggregated by subtype and age classes (<5/5–14/15–49/50–74 and 75+ yrs). As for leukemia, notable improvements in mortality and DALYs were recorded for all ages, except for the 75+ yrs one. As for ALL, the most common leukemia among children and adolescents, just these age classes recorded the largest improvements in all metrics. As for CLL, no cases were estimated up to 15 yrs of age, afterwards a significant decline in mortality and DALYs was found, except for 75+ yrs. AML metrics improved especially among the younger age classes, while severely worsened starting from the 50s yrs. CML and other leukemias achieved the greatest and most significant improvements: for all subtypes, the more favorable trends for younger patients depend on the feasibility of intense chemotherapy and bone marrow transplantation regimens, for whom elder patients cannot be candidate.

The burden of leukemia in Italy, time trends from 1990 to 2023, disaggregated by sex and age classes

Fig. 4 shows the 1990–2023 time trends for incidence, mortality and DALYs, disaggregated by sex and age classes (<5/5–14/15–49/50–74 and 75+ yrs), for leukemia at level 3. All metrics showed better performances for younger people and females, a classical phenomenon in oncology, but the time trends for the disaggregated sexes had similar profiles. As for the incidence age-standardized rate, it increased up to around 2008, starting then to progressively improve for all age classes, except for the 75+ yrs one. As for mortality rate, it was pretty stable over time for all age classes, while DALYs rate remarkably declined over time, except among the 75+ yrs people.

The burden of ALL in Italy

In 1990 and 2023, ALL accounted for 14.5–8.9% and 11.5–7.0% of leukemia new cases and deaths, respectively (Tables 1–3, Supplementary Figs. S1–S3). ALL incident cases declined over time from 1793 to 1380;

	1990			2023			1990–2023	1990–2023
	Incident cases (95% UI)	All ages incidence rate/100,000 (95% UI)	ASIR/100,000 (95% UI)	Incident cases (95% UI)	All ages incidence rate/100,000 (95% UI)	ASIR/100,000 (95% UI)	ARC for incidence rate (95% UI)	ARC for ASIR (95% UI)
Leukemia								
Italy, country	12,329 (8257–19,911)	21.70 (15.01–35.05)	17.72 (11.48–30.33)	15,586 (10,731–21,738)	26.48 (18.23–36.93)	14.17 (9.21–19.48)	0.22 (−0.26 to 1.02)	−0.20 (−0.54 to 0.43)
Italy, male	6507 (4623–9930)	23.61 (16.78–36.03)	20.21 (13.67–32.30)	8504 (5857–12,059)	29.57 (20.37–41.93)	16.77 (11.01–24.09)	0.25 (−0.23 to 1.09)	−0.17 (−0.52 to 0.44)
Italy, female	5822 (3725–9630)	19.91 (12.74–32.93)	15.97 (9.24–28.09)	7082 (4529–9870)	23.53 (15.05–32.79)	11.96 (7.11–16.63)	0.18 (−0.35 to 1.11)	−0.25 (−0.63 to 0.48)
Acute lymphoid leukemia								
Italy, country	1793 (1042–3209)	3.16 (1.83–5.65)	4.20 (2.24–8.05)	1380 (900–1763)	2.34 (1.53–3.00)	3.02 (1.74–4.05)	−0.26 (−0.59 to 0.44)	−0.28 (−0.65 to 0.50)
Italy, male	939 (551–1608)	3.41 (2.00–5.84)	4.31 (2.39–7.74)	782 (525–1048)	2.72 (1.82–3.64)	3.47 (2.07–4.89)	−0.20 (−0.57 to 0.47)	−0.20 (−0.60 to 0.64)
Italy, female	854 (442–1516)	2.92 (1.51–5.18)	4.10 (1.86–7.87)	598 (366–813)	1.99 (1.22–2.70)	2.57 (1.30–3.70)	−0.32 (−0.66 to 0.44)	−0.37 (−0.72 to 0.54)
Chronic lymphoid leukemia								
Italy, country	3887 (3147–4911)	6.84 (5.54–8.65)	4.33 (3.49–5.48)	5229 (3869–6555)	8.88 (6.57–11.14)	3.44 (2.56–4.36)	0.30 (−0.05 to 0.78)	−0.20 (−0.41 to 0.10)
Italy, male	2253 (1802–2756)	8.17 (6.54–10.00)	5.92 (4.73–7.24)	3008 (2292–3783)	10.46 (7.97–13.16)	4.54 (3.43–5.73)	0.28 (−0.06 to 0.79)	−0.23 (−0.44 to 0.07)
Italy, female	1634 (1217–2279)	5.59 (4.16–7.79)	3.16 (2.34–4.44)	2221 (1477–2991)	7.38 (4.91–9.94)	2.55 (1.72–3.50)	0.32 (−0.13 to 1.02)	−0.19 (−0.48 to 0.27)
Acute myeloid leukemia								
Italy, country	1847 (1433–2776)	3.25 (2.52–4.89)	2.56 (1.92–4.08)	5282 (3309–8763)	8.97 (5.62–14.89)	4.20 (2.55–6.87)	1.76 (0.62–4.07)	0.64 (−0.09 to 2.13)
Italy, male	936 (706–1382)	3.40 (2.56–5.02)	2.89 (2.07–4.47)	2730 (1793–4652)	9.49 (6.24–16.18)	4.84 (3.04–8.25)	1.80 (0.60–4.29)	0.68 (−0.08 to 2.25)
Italy, female	911 (672–1411)	3.12 (2.30–4.83)	2.29 (1.63–3.76)	2552 (1441–4230)	8.48 (4.79–14.05)	3.67 (2.09–6.01)	1.72 (0.44–4.36)	0.60 (−0.18 to 2.25)
Chronic myeloid leukemia								
Italy, country	3839 (1878–7445)	6.76 (3.31–13.11)	5.50 (2.55–10.82)	2809 (1546–3984)	4.77 (2.63–6.77)	2.89 (1.54–4.22)	−0.29 (−0.69 to 0.61)	−0.48 (−0.78 to 0.28)
Italy, male	1847 (923–3614)	6.70 (3.35–13.11)	5.63 (2.73–11.15)	1451 (718–2341)	5.05 (2.50–8.14)	3.09 (1.43–5.13)	−0.25 (−0.68 to 0.80)	−0.45 (−0.78 to 0.39)
Italy, female	1992 (906–3859)	6.81 (3.10–13.20)	5.50 (2.35–10.79)	1357 (760–1986)	4.51 (2.52–6.60)	2.73 (1.44–4.07)	−0.34 (−0.72 to 0.55)	−0.50 (−0.79 to 0.28)
Other leukemia								
Italy, country	963 (803–1154)	1.69 (1.41–2.03)	1.14 (0.95–1.38)	887 (690–1127)	1.51 (1.17–1.91)	0.62 (0.48–0.79)	−0.11 (−0.35 to 0.21)	−0.46 (−0.60 to −0.26)
Italy, male	532 (409–664)	1.93 (1.49–2.41)	1.45 (1.11–1.82)	533 (381–719)	1.85 (1.32–2.50)	0.83 (0.59–1.14)	−0.05 (−0.39 to 0.39)	−0.43 (−0.63 to −0.16)
Italy, female	430 (334–540)	1.47 (1.14–1.85)	0.91 (0.71–1.14)	354 (248–468)	1.18 (0.82–1.56)	0.44 (0.31–0.58)	−0.20 (−0.44 to 0.14)	−0.52 (−0.66 to −0.31)

Table 1: **Incident cases, crude and age-standardized incidence rates (ASIRs) of leukemia, with annualized rate of change (ARC) and 95% Uncertainty Intervals (UIs) in 1990 and 2023, Italy national estimates.**

	1990			2023			1990–2023	1990–2023	1990	2023
	Death cases (95% UI)	All ages death rate/ 100,000 (95% UI)	ASMR/100,000 (95% UI)	Death cases (95% UI)	All ages death rate/ 100,000 (95% UI)	ASMR/100,000 (95% UI)	Annual rate of change for death rate (95% UI)	Annual rate of change for ASMR (95% UI)	ASMIR	ASMIR
Leukemia										
Italy, country	5502 (5057–5957)	9.69 (8.90–10.49)	6.82 (6.23–7.43)	7100 (6053–7856)	12.06 (10.28–13.35)	4.69 (4.09–5.19)	0.25 (0.10–0.40)	−0.31 (−0.39 to −0.22)	38.5	33.1
Italy, male	3006 (2693–3290)	10.91 (9.77–11.94)	8.78 (7.81–9.68)	3943 (3392–4453)	13.71 (11.79–15.48)	6.06 (5.28–6.84)	0.26 (0.08–0.47)	−0.31 (−0.41 to −0.19)	43.4	36.1
Italy, female	2496 (2180–2778)	8.53 (7.45–9.50)	5.45 (4.82–6.08)	3157 (2445–3704)	10.49 (8.12–12.30)	3.63 (2.92–4.18)	0.23 (0.00–0.44)	−0.33 (−0.45 to −0.22)	34.1	30.4
Acute lymphoid leukemia										
Italy, country	634 (544–728)	1.12 (0.96–1.28)	1.11 (0.96–1.29)	494 (403–581)	0.84 (0.68–0.99)	0.56 (0.48–0.66)	−0.25 (−0.41 to −0.07)	−0.50 (−0.60 to −0.38)	26.4	18.5
Italy, male	350 (290–425)	1.27 (1.05–1.54)	1.30 (1.07–1.58)	267 (205–323)	0.93 (0.71–1.12)	0.68 (0.53–0.82)	−0.27 (−0.46 to −0.03)	−0.48 (−0.61 to −0.31)	30.2	19.6
Italy, female	284 (232–342)	0.97 (0.79–1.17)	0.94 (0.77–1.13)	226 (172–289)	0.75 (0.57–0.96)	0.45 (0.35–0.56)	−0.22 (−0.42 to 0.05)	−0.52 (−0.64 to −0.35)	22.9	17.5
Chronic lymphoid leukemia										
Italy, country	1429 (1257–1603)	2.52 (2.21–2.82)	1.55 (1.36–1.74)	1811 (1441–2091)	3.08 (2.45–3.55)	0.94 (0.76–1.08)	0.22 (0.01–0.45)	−0.39 (−0.50 to −0.29)	35.8	27.3
Italy, male	832 (724–968)	3.02 (2.63–3.51)	2.31 (2.00–2.70)	982 (794–1170)	3.42 (2.76–4.07)	1.31 (1.06–1.56)	0.13 (−0.09 to 0.42)	−0.43 (−0.54 to −0.28)	39.0	28.9
Italy, female	597 (507–694)	2.04 (1.73–2.37)	1.06 (0.90–1.24)	829 (602–1032)	2.75 (2.00–3.43)	0.69 (0.52–0.86)	0.35 (0.04–0.70)	−0.35 (−0.51 to −0.19)	33.5	27.1
Acute myeloid leukemia										
Italy, country	1504 (1336–1693)	2.65 (2.35–2.98)	1.90 (1.67–2.15)	3441 (2977–3897)	5.85 (5.06–6.62)	2.39 (2.12–2.69)	1.21 (0.91–1.60)	0.26 (0.07–0.49)	74.2	56.9
Italy, male	771 (658–889)	2.80 (2.39–3.22)	2.22 (1.87–2.58)	1925 (1656–2217)	6.69 (5.76–7.71)	2.99 (2.58–3.43)	1.39 (0.96–1.91)	0.35 (0.11–0.65)	76.8	61.8
Italy, female	733 (621–853)	2.51 (2.13–2.92)	1.65 (1.41–1.93)	1516 (1176–1812)	5.04 (3.91–6.02)	1.91 (1.55–2.28)	1.01 (0.59–1.56)	0.15 (−0.09 to 0.47)	72.1	52.0
Chronic myeloid leukemia										
Italy, country	1147 (974–1357)	2.02 (1.72–2.39)	1.37 (1.16–1.63)	575 (439–701)	0.98 (0.75–1.19)	0.46 (0.27–0.42)	−0.52 (−0.63 to −0.38)	−0.75 (−0.81 to −0.68)	24.9	15.9
Italy, male	629 (508–778)	2.28 (1.84–2.82)	1.79 (1.44–2.22)	320 (249–398)	1.11 (0.87–1.38)	0.46 (0.36–0.57)	−0.51 (−0.64 to −0.35)	−0.74 (−0.81 to −0.66)	31.8	14.9
Italy, female	518 (401–652)	1.77 (1.37–2.23)	1.09 (0.83–1.37)	255 (172–701)	0.85 (0.57–1.14)	0.26 (0.18–0.35)	−0.52 (−0.69 to −0.32)	−0.76 (−0.84 to −0.66)	19.8	9.5
Other leukemia										
Italy, country	787 (666–905)	1.39 (1.17–1.59)	0.89 (0.75–1.02)	780 (626–969)	1.32 (1.06–1.65)	0.46 (0.37–0.57)	−0.04 (−0.24 to 0.28)	−0.49 (−0.59 to −0.30)	78.1	74.2
Italy, male	423 (345–523)	1.54 (1.25–1.90)	1.16 (0.94–1.44)	448 (335–589)	1.56 (1.16–2.05)	0.63 (0.47–0.84)	0.02 (−0.27 to 0.45)	−0.46 (−0.61 to −0.23)	80.0	75.9
Italy, female	364 (275–453)	1.25 (0.94–1.55)	0.70 (0.54–0.88)	331 (239–969)	1.10 (0.79–1.48)	0.33 (0.25–0.43)	−0.12 (−0.36 to 0.29)	−0.54 (−0.66 to −0.32)	76.9	75.0

Table 2: **Death cases, crude and age-standardized mortality rates (ASMRs) of leukemia, with 95% Uncertainty Intervals (UIs) and age-standardized mortality to incidence ratio (ASMIR), in 1990 and 2023, Italy national estimates.**

	1990			2023			1990–2023	1990–2023
	DALYs (95% UI)	All ages DALYs rate/ 100,000 (95% UI)	ASDR/100,000 (95% UI)	DALYs (95% UI)	All ages DALYs rate/ 100,000 (95% UI)	ASDR/100,000 (95% UI)	ARC for DALYs rate (95% UI)	ARC for ASDR (95% UI)
Leukemia								
Italy, country	156,663 (140,890–170,206)	275.80 (248.03–299.64)	234.08 (206.63–257.70)	136,708 (120,237–151,238)	232.26 (204.28–256.95)	128.15 (114.59–142.58)	−0.16 (−0.26 to −0.03)	−0.45 (−0.52 to −0.36)
Italy, male	88,703 (76,665–99,001)	321.84 (278.17–359.21)	284.64 (244.73–319.89)	78,623 (68,528–89,012)	273.39 (238.29–309.52)	158.72 (137.76–182.73)	−0.15 (−0.27 to 0.03)	−0.44 (−0.53 to −0.31)
Italy, female	67,960 (60,192–77,307)	232.40 (205.83–264.36)	191.90 (168.59–220.91)	58,085 (46,257–67,325)	192.97 (153.67–223.66)	101.21 (84.40–117.46)	−0.17 (−0.33 to −0.01)	−0.47 (−0.57 to −0.36)
Acute lymphoid leukemia								
Italy, country	32,410 (27,907–37,485)	57.06 (49.13–65.99)	68.65 (59.12–79.07)	15,847 (13,430–18,495)	26.92 (22.82–31.42)	29.19 (24.72–34.06)	−0.53 (−0.62 to −0.42)	−0.57 (−0.66 to −0.47)
Italy, male	18,885 (15,456–23,424)	68.52 (56.08–84.99)	79.66 (64.82–98.77)	9274 (7346–11,379)	32.25 (25.54–39.57)	35.20 (27.70–42.92)	−0.53 (−0.65 to −0.37)	−0.56 (−0.67 to −0.41)
Italy, female	13,525 (11,258–16,550)	46.25 (38.50–56.60)	57.46 (47.66–70.12)	6573 (5101–8220)	21.84 (16.95–27.31)	22.99 (18.07–28.79)	−0.53 (−0.65 to −0.36)	−0.60 (−0.71 to −0.47)
Chronic lymphoid leukemia								
Italy, country	29,907 (26,614–33,459)	52.65 (46.85–58.90)	33.22 (29.38–37.34)	28,526 (23,218–33,229)	48.47 (39.45–56.46)	17.32 (14.20–19.99)	−0.08 (−0.25 to 0.10)	−0.48 (−0.57 to −0.37)
Italy, male	18,284 (15,527–21,537)	66.34 (56.34–78.14)	48.51 (41.17–57.30)	16,600 (13,197–19,650)	57.72 (45.89–68.33)	24.00 (19.07–28.41)	−0.13 (−0.31 to 0.13)	−0.51 (−0.61 to −0.36)
Italy, female	11,623 (9822–13,749)	39.75 (33.59–47.02)	22.05 (18.50–26.42)	11,926 (8753–15,140)	39.62 (29.08–50.30)	12.05 (9.11–15.36)	0.00 (−0.24 to 0.28)	−0.45 (−0.58 to −0.29)
Acute myeloid leukemia								
Italy, country	45,121 (39,564–51,321)	79.43 (69.65–90.35)	68.08 (59.24–78.20)	69,177 (61,482–77,925)	117.53 (104.46–132.39)	63.99 (57.84–72.53)	0.48 (0.26–0.77)	−0.06 (−0.22 to 0.14)
Italy, male	24,062 (20,036–28,615)	87.31 (72.70–103.82)	77.27 (63.81–93.58)	39,196 (33,736–44,981)	136.29 (117.31–156.41)	76.71 (65.58–89.03)	0.56 (0.27–0.96)	0.00 (−0.21 to 0.28)
Italy, female	21,058 (17,872–24,795)	72.01 (61.11–84.79)	60.09 (49.96–71.87)	29,981 (24,077–35,701)	99.60 (79.99–118.60)	52.78 (43.68–63.42)	0.38 (0.08–0.79)	−0.12 (−0.31 to 0.15)
Chronic myeloid leukemia								
Italy, country	31,240 (26,160–37,579)	55.00 (46.05–66.16)	42.25 (35.17–51.29)	10,205 (7870–12,552)	17.34 (13.37–21.33)	8.28 (6.36–10.21)	−0.68 (−0.76 to −0.59)	−0.80 (−0.85 to −0.74)
Italy, male	17,558 (14,029–22,165)	63.71 (50.90–80.42)	51.94 (41.38–66.01)	5817 (4934–7400)	20.23 (15.28–25.73)	10.34 (7.82–13.45)	−0.68 (−0.77 to −0.56)	−0.80 (−0.86 to −0.72)
Italy, female	13,681 (10,427–17,112)	46.79 (35.66–58.52)	34.36 (25.73–43.38)	4388 (3065–5871)	14.58 (10.18–19.51)	6.61 (4.75–8.88)	−0.69 (−0.80 to −0.54)	−0.81 (−0.87 to −0.71)
Other leukemia								
Italy, country	17,986 (14,992–20,930)	31.66 (26.39–36.85)	21.89 (18.15–25.67)	12,953 (10,434–15,967)	22.01 (17.73–27.13)	9.35 (7.57–11.55)	−0.30 (−0.45 to −0.06)	−0.57 (−0.66 to −0.41)
Italy, male	9913 (7830–12,239)	35.97 (28.41–44.41)	27.26 (21.39–33.73)	7736 (5827–10,383)	26.90 (20.26–36.11)	12.48 (9.42–16.88)	−0.25 (−0.46 to 0.09)	−0.54 (−0.67 to −0.33)
Italy, female	8073 (6359–9952)	27.61 (21.74–34.03)	17.94 (14.14–22.33)	5217 (3891–6876)	17.33 (12.93–22.84)	6.77 (5.10–8.79)	−0.37 (−0.55 to −0.08)	−0.62 (−0.72 to −0.44)

Table 3: **Disability-Adjusted Life Years (DALYs), crude and age-standardized DALYs rates (ASDR) of leukemia, with annualized rate of change (ARC) and 95% Uncertainty Intervals (UIs), in 1990 and 2023, Italy national estimates.**

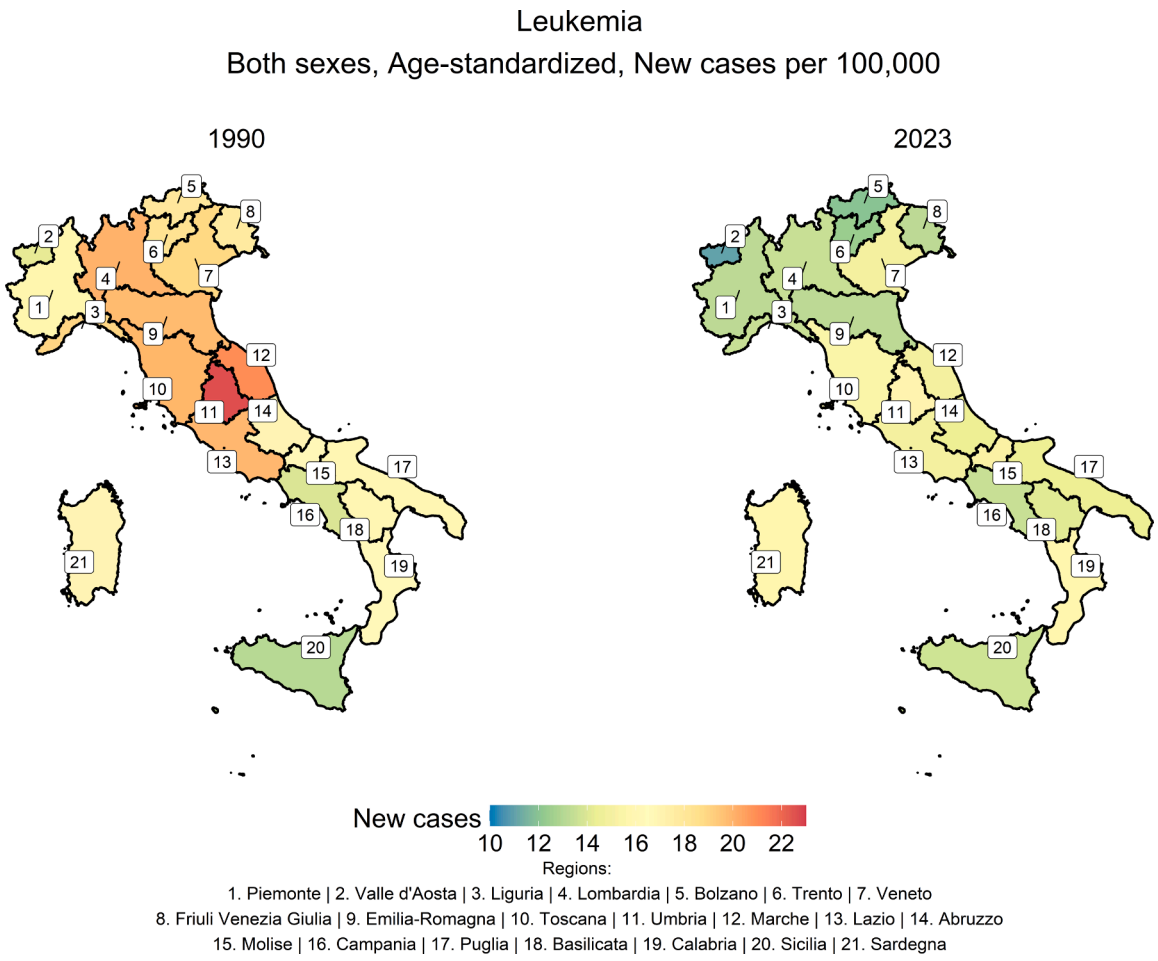

Fig. 1: Leukemia, both sexes, age-standardized, 1990–2023, new cases per 100,000 population.

the ASIR moved from 4.20 (2.24–8.05) to 3.02 (1.74–4.05), with a stable ARC (–0.28; –0.65 to 0.50). As for mortality, 634 and 494 persons died by ALL, with a marked improvement in ASMR from 1.11 (0.96–1.29) to 0.56 (0.48–0.66) and a significant ARC equal to –0.50 (–0.60 to –0.38). The ASMIR showed a consequent improvement over time (from 26.4 to 18.5), with a larger improvement for males (from 30.2 to 19.6) than for females (from 22.9 to 17.5). The DALYs count estimates halved over time from 32,410 to 15,847 DALYs, respectively. The ASDR dropped from 68.65 (59.12–79.07) to 29.19 (24.72–34.06), with a significantly negative ARC of –0.57 (–0.66 to –0.47). No sex-related significant differences emerged for the ALL estimates.

The burden of CLL in Italy

In 1990 and 2023, CLL accounted for 31.5–33.5% and 26.0–25.5% of leukemia new cases and deaths, respectively (Tables 1–3, Supplementary Figs. S4–S6). CLL incident cases increased over time from 3887 to 5,229, while the ASIR was almost stable from 4.33 (3.49–5.48) to 3.44 (2.56–4.36), with a non-significant ARC (–0.20; –0.41 to 0.10). As for mortality, 1429 and 1811 persons died by CLL, with a great improvement in ASMR from 1.55 (1.36–1.74) to 0.94 (0.76–1.08) and a significantly ARC of –0.39 (–0.50 to –0.29). The ASMIR had a remarkable improvement over time (from 35.8 to 27.3), with a larger recovery for males (from 39.0 to 28.9) than for females (from 33.5 to 27.1). As for DALYs count estimates, 29,907 and 28,526 DALYs were caused by CLL in 1990 and 2023, respectively; the ASDR nearly halved from 33.22 (29.38–37.34) to 17.32 (14.20–19.99), with a significant ARC of –0.48 (–0.57 to –0.37). No other sex-related differences emerged for the CLL estimates.

The burden of AML in Italy

In 1990 and 2023, AML accounted for 15.0–33.9% and 27.3–48.5% of leukemia new cases and deaths, respectively (Tables 1–3, Supplementary Figs. S7–S9). AML incident cases trebled over time, from 1847 to 5282. The

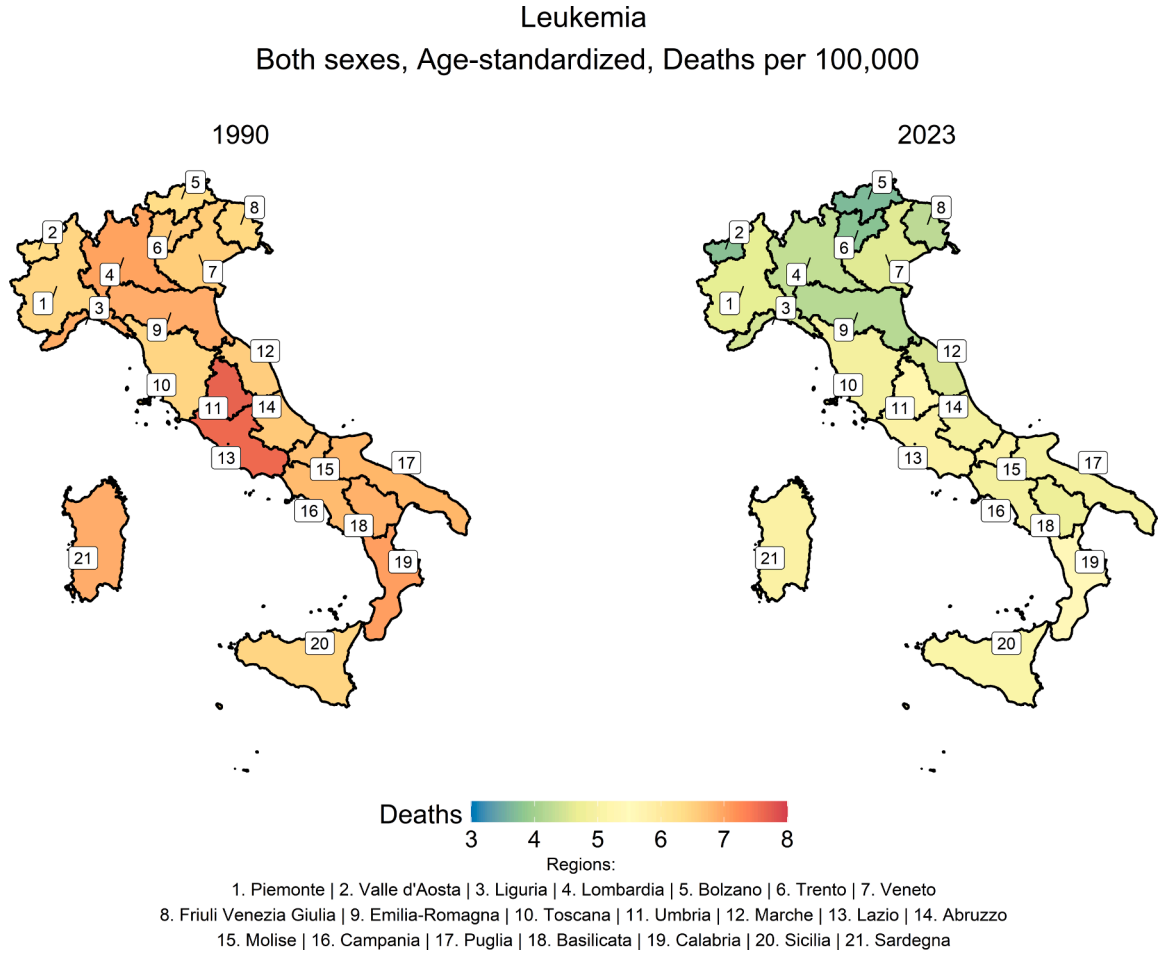

Fig. 2: Leukemia, both sexes, age-standardized, 1990–2023, deaths per 100,000 population.

ASIR was 2.56 (1.92–4.08) in 1990 and 4.20 (2.55–6.87) in 2023, with a non-significant ARC (+0.64; –0.09 to 2.13). As for mortality, 1504 and 3441 persons died of AML, with the ASMR rising from 1.90 (1.67–2.15) to 2.39 (2.12–2.69) and a significant ARC (+0.26; 0.07 to 0.49). The age-standardized MIR declined over time (from 74.2 to 56.9), confirming its severe prognosis. As for DALYs count estimates, 45,121 and 69,177 DALYs were caused by AML in 1990 and 2023, respectively. The ASDR was stable from 68.08 (59.24–78.20) in 1990 to 63.99 (57.84–72.53) in 2023, with an ARC equal to –0.06 (–0.22 to 0.14).

The burden of CML in Italy

In 1990 and 2023, CML accounted for 31.1–18.0% and 20.8–8.1% of leukemia new cases and deaths, respectively (Tables 1–3, Supplementary Figs. S10–S12). CML incident cases remarkably declined over time from 3839 to 2809; however, the ASIR was 5.50 (2.55–10.82) in 1990 and 2.89 (1.54–4.22) in 2023, indicating a non-significant change over time (ARC –0.48; –0.78 to 0.28). As for mortality, 1147 and 575 persons died by CML, with a huge improvement in ASMR, from 1.37 (1.16–1.63) to 0.46 (0.27–0.42) and a highly significant ARC of –0.75 (–0.81 to –0.68). The ASMIR showed a consequent improvement over time (from 24.9 to 15.9). As for DALYs estimates, 31,240 and 10,205 DALYs were caused by CML in 1990 and 2023, respectively; the ASDR dropped from 42.25 (35.17–51.29) to 8.28 (6.36–10.21), with a highly significant ARC equal to –0.80 (–0.85 to –0.74). No sex-related difference emerged for the CML estimates.

The burden of other leukemia in Italy

In 1990 and 2023, other leukemia accounted for 7.8–5.7% and 14.3–11.0% of leukemia new cases and deaths, respectively (Tables 1–3, Supplementary Figs. S13–S15). At level 4, the incidence of rare leukemias belonging to different histotypes declined: the incident cases reduced from 963 to 887, their ASIR halved from 1.14 (0.95–1.38) to 0.62 (0.48–0.79), with a significant ARC of –0.46 (–0.60 to –0.26). Mortality was

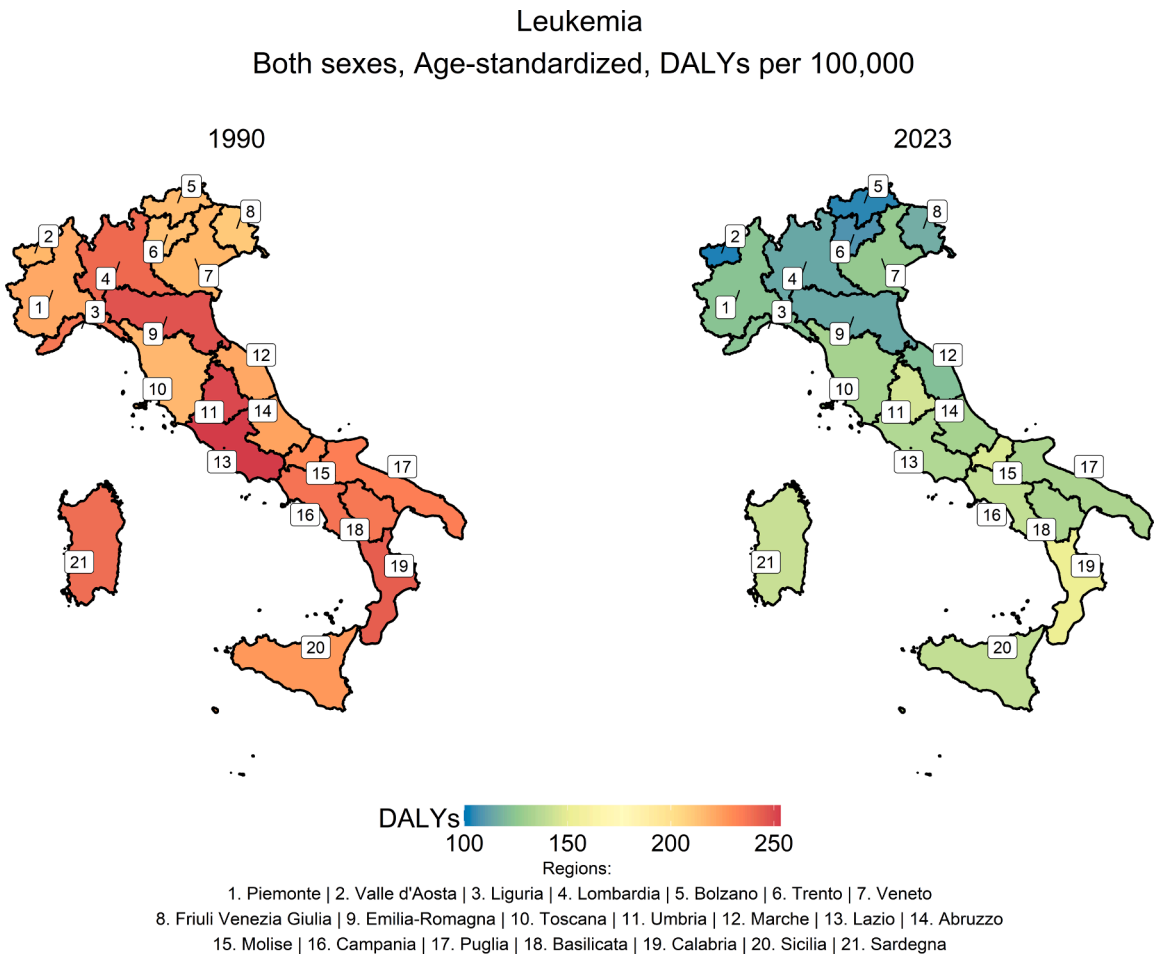

Fig. 3: Leukemia, both sexes, age-standardized, 1990–2023, DALYs per 100,000 population.

quite stable from 787 to 780 cases, but the ASMR ranged from 0.89 (0.75–1.02) to 0.46 (0.37–0.57), with a highly significant ARC of –0.49 (–0.59 to –0.30). Nevertheless, this heterogeneous group of diseases still has a severe prognosis, as proven by a stable MIR over time (78.1 and 74.2). As for the ASDR, it strongly improved from 21.89 (18.15–25.67) to 9.35 (7.57–11.55), with an ARC equal to –0.57 (–0.66 to –0.41). In general, females had more favorable trends in the 1990–2023 ARCs for ASIR, ASMR and ASDR, except for the ASMIR.

Discussion

Leukemia is a multifactorial disease, with deep interactions between environmental and genetic factors, often progressing in sequential steps. Great advances have been made over time: not only in treatment options but even in cytogenetic, molecular and immunophenotypic diagnostics, to discover chromosomal abnormalities, gene mutations and antigenic alterations. Leukemia incidence strongly varies by subtypes: characterized by lymphoid or myeloid lineages that affect blood mature cells, blood precursors or both, sometimes they are hardly classifiable, especially the rarest ones. The widely recognized determinants of leukemia are smoking and parental tobacco use, high BMI, age, male sex, racial differences, genetic disorders like *Down syndrome*, familiarity, exposure to ionizing radiations, exposure to carcinogens like herbicides and pesticides, and indoor air pollutants like benzene and formaldehyde, previous chemo- and radio-therapy treatments, previous viral infections (EBV and HTLV-III), immunodeficiency disorders. For each leukemia subtype, the GBD 2023 estimated the percentage of DALYs attributable to the top risk factors, identifying as such two major risks (smoking and high BMI) and a minor one (occupational exposure to benzene and formaldehyde).

Several researches have been dedicated to the generalities of leukemia epidemiology and its risk factors.[13–16] Indeed, the main clinico-pathological guidelines for leukemia have been extensively updated

	1990		2023		1990–2023
	Death cases (95% UI)	ASMR/100,000 (95% UI)	Death cases (95% UI)	ASMR/100,000 (95% UI)	Annual rate of change for ASMR (95% UI)
Deaths, all causes					
Italy, country	543,862 (542,015–545,502)	643.97 (641.98–646.01)	672,381 (669,640–674,604)	389.37 (387.56–390.97)	−0.40 (−0.40 to −0.39)
Italy, male	282,174 (281,025–283,290)	840.95 (837.27–844.20)	325,749 (324,052–327,270)	483.01 (480.12–485.63)	−0.43 (−0.43 to −0.42)
Italy, female	261,688 (260,306–262,971)	501.11 (498.66–503.54)	346,632 (345,026–348,332)	314.90 (313.23–316.64)	−0.37 (−0.38 to −0.37)
Deaths, neoplasms					
Italy, country	156,943 (147,700–162,258)	177.97 (167.82–183.76)	190,175 (167,718–202,985)	121.51 (110.22–128.20)	−0.32 (−0.35 to −0.29)
Italy, male	92,224 (88,710–94,698)	248.83 (238.47–256.44)	104,673 (95,800–110,541)	153.25 (141.54–161.34)	−0.38 (−0.42 to −0.36)
Italy, female	64,719 (58,361–68,624)	127.92 (116.77–134.91)	85,502 (71,456–94,206)	98.18 (86.06–105.45)	−0.23 (−0.27 to −0.19)
Deaths, Leukemia					
Italy, country	5502 (5057–5957)	6.82 (6.23–7.43)	7100 (6053–7856)	4.69 (4.09–5.19)	−0.31 (−0.39 to −0.22)
Italy, male	3006 (2693–3290)	8.78 (7.81–9.68)	3943 (3392–4453)	6.06 (5.28–6.84)	−0.31 (−0.41 to −0.19)
Italy, female	2496 (2180–2778)	5.45 (4.82–6.08)	3157 (2445–3704)	3.63 (2.92–4.18)	−0.33 (−0.39 to −0.22)
	DALYs (95% UI)	**ASDR/100,000 (95% UI)**	**DALYs (95% UI)**	**ASDR/100,000 (95% UI)**	**Annual rate of change for ASDR (95% UI)**
DALYs, all causes					
Italy, country	18,321,943 (16,615,534–20,312,030)	25347.95 (22842.31–28310.88)	19,080,532 (17,020,178–21,518,319)	18618.01 (16095.77–21776.03)	−0.26 (−0.30 to −0.23)
Italy, male	9,610,791 (8,877,658–10,466,577)	29470.65 (27157.70–32201.12)	9,386,881 (8,483,322–10,413,100)	19755.56 (17419.11–22476.07)	−0.33 (−0.36 to −0.30)
Italy, female	8,711,152 (7,726,592–9,825,818)	22019.75 (19267.42–25196.70)	9,693,651 (8,509,820–11,112,202)	17847.28 (17984.26–21337.50)	−0.19 (−0.23 to −0.15)
DALYs, neoplasms					
Italy, country	3,766,185 (3,606,528–3,882,986)	4581.91 (4400.58–4719.09)	3,671,819 (3,353,036–3,869,351)	2885.90 (2698.58–3017.50)	−0.37 (−0.39 to −0.35)
Italy, male	2,252,538 (2,183,790–2,310,179)	6087.38 (5901.55–6250.04)	2,023,233 (1,893,443–2,115,095)	3395.78 (3203.85–3550.53)	−0.44 (−0.47 to −0.42)
Italy, female	1,513,647 (1,406,916–1,587,872)	3416.84 (3223.54–3571.96)	1,648,586 (1,451,608–1,768,585)	2479.88 (2282.99–2630.58)	−0.27 (−0.31 to −0.24)
DALYs, Leukemia					
Italy, country	156,663 (140,890–170,206)	234.08 (206.63–257.70)	136,708 (120,237–151,238)	128.15 (114.59–142.58)	−0.45 (−0.52 to −0.36)
Italy, male	88,703 (76,665–99,001)	284.64 (244.73–319.89)	78,623 (68,528–89,012)	158.72 (137.76–182.73)	−0.44 (−0.53 to −0.31)
Italy, female	67,960 (60,192–77,307)	191.90 (168.59–220.91)	58,085 (46,257–67,325)	101.21 (84.40–117.46)	−0.47 (−0.57 to −0.36)

Table 4: **Mortality and Disability-Adjusted Life Years (DALYs) for all causes, neoplasms and leukemia, with annualized rate of change (ARC) and 95% Uncertainty Intervals (UIs), in 1990 and 2023, Italy national estimates.**

Leukemia-incidence	1990	2023	1990–2023
	ASIR/100,000 (95% UI)	ASIR/100,000 (95% UI)	ARC (95% UI)
Global	8.66 (7.40–10.80)	6.70 (5.18–8.69)	−0.23 (−0.43 to 0.09)
High-middle SDI countries	7.57 (6.46–8.81)	5.88 (4.52–7.89)	−0.22 (−0.41 to 0.16)
Italy, country	17.72 (11.48–30.33)	14.17 (9.21–19.48)	−0.20 (−0.54 to 0.43)
Leukemia-mortality	**ASMR/100,000 (95% UI)**	**ASMR/100,000 (95% UI)**	**ARC (95% UI)**
Global	5.94 (5.29–6.57)	3.95 (3.55–4.45)	−0.34 (−0.41 to −0.24)
High-middle SDI countries	6.08 (5.15–6.89)	3.53 (3.12–4.09)	−0.42 (−0.50 to −0.30)
Italy, country	6.82 (6.23–7.43)	4.69 (4.09–5.19)	−0.31 (−0.39 to −0.22)
Leukemia-YLDs	**ASYLD/100,000 (95% UI)**	**ASYLD/100,000 (95% UI)**	**ARC (95% UI)**
Global	3.86 (2.50–5.89)	3.35 (2.11–4.99)	−0.13 (−0.42 to 0.34)
High-middle SDI countries	3.10 (2.11–4.46)	3.00 (1.85–4.78)	−0.03 (−0.35 to 0.60)
Italy, country	9.48 (5.19–17.26)	7.91 (4.12–11.99)	−0.17 (−0.55 to 0.61)
Leukemia-YLLs	**ASYLL/100,000 (95% UI)**	**ASYLL/100,000 (95% UI)**	**ARC (95% UI)**
Global	246.08 (209.85–276.75)	144.57 (126.09–167.82)	−0.41 (−0.50 to −0.31)
High-middle SDI countries	295.02 (247.00–331.11)	148.86 (132.16–171.44)	−0.50 (−0.56 to −0.39)
Italy, country	224.60 (200.19–245.51)	120.23 (108.39–133.14)	−0.46 (−0.53 to −0.38)
Leukemia-DALYs	**ASDR/100,000 (95% UI)**	**ASDR/100,000 (95% UI)**	**ARC (95% UI)**
Global	249.94 (213.94–280.11)	147.92 (130.32–171.39)	−0.41 (−0.49 to −0.31)
High-middle SDI countries	298.12 (249.88–334.23)	151.86 (135.50–175.17)	−0.49 (−0.56 to −0.38)
Italy, country	234.08 (206.63–257.70)	128.15 (114.59–142.58)	−0.45 (−0.52 to −0.36)

Table 5: **Age-standardized incidence (ASIR), mortality (ASMR), YLDs (ASYLD), YLLs (ASYLL) and DALYs (ASDR) rates for leukemia, with annualized rate of change (ARC) and 95% Uncertainty Intervals (UIs), in 1990 and 2023, Italy national vs. Global vs. High-middle SDI countries estimates.**

in the last years: the 5th edition of the WHO Classification of Haematolymphoid Tumours for Myeloid[17] and Lymphoid Neoplasms,[18] the International Consensus Classification of Myeloid[19] and Lymphoid Neoplasms,[20] the Clinical Practice Guidelines from the National Comprehensive Cancer Center.[21–24] More specifically, both the epidemiology and the clinical management and survivorship for each of the main leukemia subtypes have been covered by studies focused on ALL,[25–29] CLL,[30–34] AML[35–39] and CML,[40–44] respectively. While several GBD publications investigated the burden of cancer and risk factors at the global, regional and national levels,[45–50] no official GBD leukemia-dedicated study has been published yet. Recently, independent researchers explored the burden of leukemia, based on GBD 2017,[51–54] GBD 2019[55–59] and GBD 2021 estimates.[60–62] Moreover, the global patterns of leukemia have been recently investigated by researchers from the International Agency for Research on Cancer, using the Globocan 2022 database.[63]

Some national data sources on leukemia are available for Italy: the I.Stat database from the Istituto Nazionale di Statistica-ISTAT,[64] the cancer registry database from the Associazione Italiana Registri Tumori-AIRTUM[65] and the volume "I numeri del cancro in Italia" from the Associazione Italiana di Oncologia Medica-AIOM.[66] The Italian health performance and burden of cancer have also been covered by the publications of the Italian GBD Initiative, relative to GBD 2017.[67,68]

Following the GBD 2023 estimates, the burden of oncohematological neoplasms in Italy – including Hodgkin and Non-Hodgkin Lymphoma (NHL), multiple myeloma (MM) and leukemia – accounted for 43,000 new cases and 17,700 deaths in 2023, with a mortality-to-incidence ratio equal to 41.2. Of them, leukemia accounted for 15,600 new cases (36.3%) and 7100 deaths (40.1%), with a mortality-to-incidence ratio equal to 33.1. Even more impressive, 237,800 population are estimated to live in Italy with an oncohematological neoplasm, 69,800 of them with leukemia (29.4%): these data prove how challenging is the fight against leukemia.

Of note, the burden of leukemia at the national level showed a favourable and significant declining trend for the age-standardized mortality and DALYs: the 1990–2023 ARC for ASMR and ASDR were equal to –0.31 and –0.45 respectively, while that for ASIR had only marginal improvements (–0.20). As for incidence, the NHL and MM trends showed comparable and marginal tendencies (ARC +0.20 and + 0.28), while HL had a significant improvement over time (ARC –0.26). As for mortality and DALYs, both NHL (ARC –0.21 and –0.33) and HL (ARC –0.59 and –0.64) trends significantly improved over time, while MM was stable (ARC +0.04 and –0.07).

In recent years, the global burden of leukemia underwent major changes, depending on subtypes. In most cases, the current analysis confirms at the Italian level the GBD Global trends. Huge advances involved

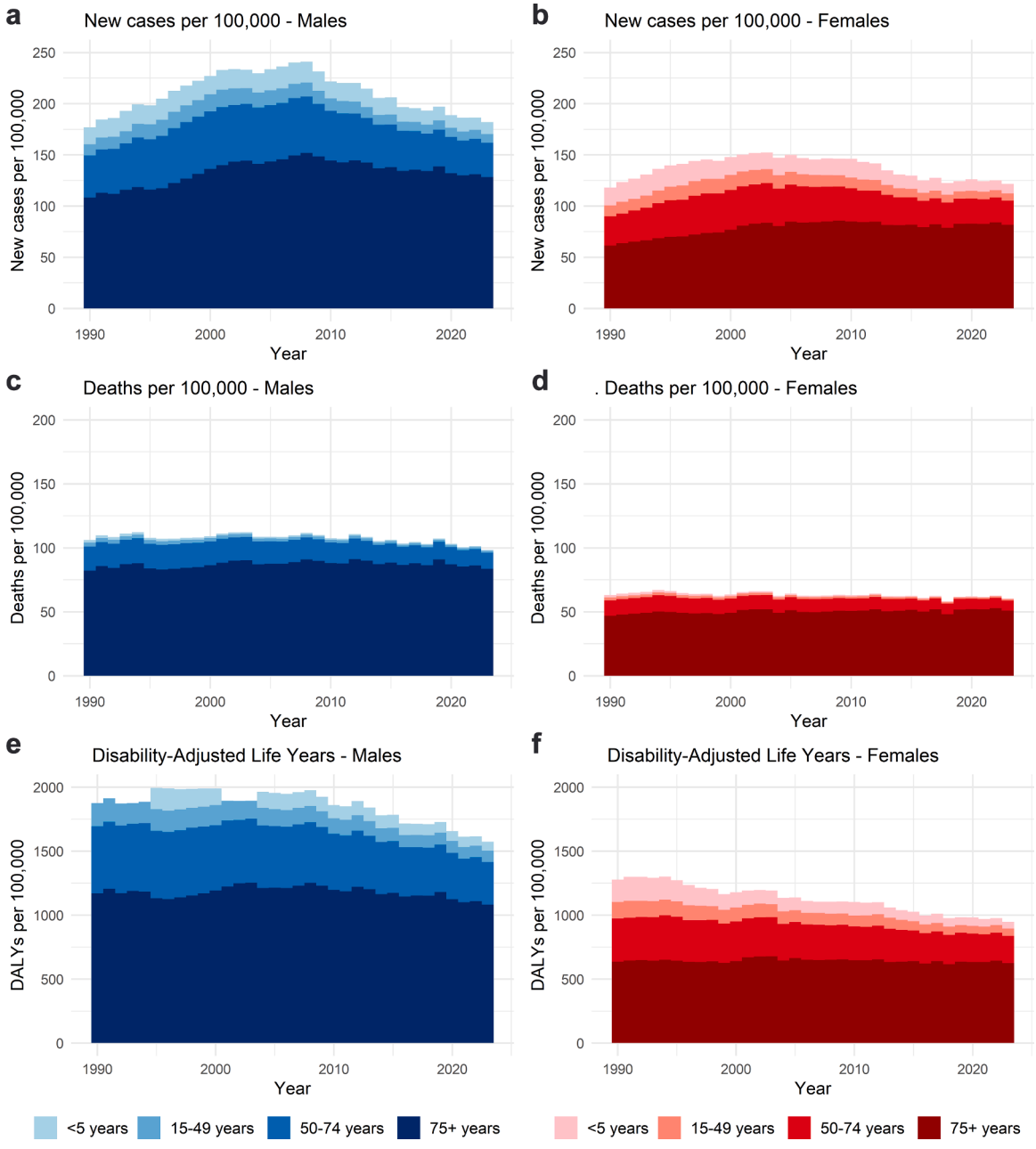

Fig. 4: Leukemia, 1990–2023 time trends for incidence (a, b), mortality (c, d) and DALYs (e, f), disaggregated by sex and age classes (<5/5–14/15–49/50–74/75+ yrs).

both leukemia-related survival (as the age-standardized MIR suggests) and morbidity (as the trend for DALYs demonstrates): wider improvements happened among females. As for the declines in other leukemia, they may be due to improved classification over time, too. A couple of differences, between Italy versus the GBD Global and High-middle SDI countries, came to attention: a worrying scenario for the increased AML incidence and mortality in Italy (depending on ageing, smoking and occupational exposure/environmental risks), a promising one for the stable national incidence of CLL, which on the contrary significantly rose in High-middle SDI countries. In general, Italy showed consistently higher age-standardized incidence rates of leukemia across the time period considered compared to high-middle SDI countries. While the annual rate of

change in incidence was similar across all groups, the higher baseline in Italy may reflect differences in health system infrastructure, cancer registration coverage, and case detection. Conversely, age-standardized mortality and DALY rates in Italy are broadly comparable to those in other high-middle SDI countries, suggesting similar effectiveness in treatment and management. However, given the heterogeneity of the comparison groups and the complexity of factors involved, it remains difficult to speculate with certainty on the drivers behind these differences. As for the leukemia Italian estimates, few sex-related differences emerged, well considering the reduced incidence, mortality and DALYs typically reported for females in oncology. The only exception was the ARC for AML-related ASMR: the mortality tendency was stable among females (0.15), while worsening among males (0.35). The reasons for this sex-specific pattern are not fully understood, and further research is needed to clarify the underlying mechanisms.

Sex-based differences in prognosis have been widely reported across leukemia subtypes, including AML, with females generally showing improved survival compared to males. This survival advantage may be partly explained by sex-specific molecular features, such as a higher prevalence of favourable mutations (e.g., FLT3, NPM1, DNMT3A) in females, as well as potentially stronger immune responses and hormonal influences. Behavioural and healthcare engagement differences may also contribute. However, these factors do not uniformly explain all outcome disparities. Indeed, recent sex-stratified analyses of clinical trials in AML have revealed inconsistent patterns, with some treatments conferring greater benefit in males and others in females. This highlights the complexity of sex-related mechanisms in AML and the need for more targeted investigation to inform sex-specific therapeutic strategies.[69] These determinants add to the risk deriving from previous chemo-/radio-therapy regimens, which can give raise to t-AMLs (therapy-related AMLs, according to the WHO classification). As for CML, the GBD 2023 estimates show a quite consistent drop in both morbidity and mortality, depending on the introduction of Tyrosine Kinase Inhibitors (TKIs), which revolutionized CML therapy. Imatinib, the first TKI, was approved by the FDA in 2001 and now it is on the WHO List of Essential Medicines. Six TKIs are actually approved for CML treatment in Italy, where the best GBD estimates occurred.

A final consideration has to be posed about the study limitations. First, the large number of leukemia subtypes complicates the analysis of the subnational local burden of disease. Second, the GBD 2023 only considers two main risk factors (high BMI and smoking) and two minor ones (occupational exposures to benzene and formaldehyde). These determinants account for only 15% of leukemia-related DALYs: further evidence is needed to increase the number and relevance of risk factors attributable to leukemia, at the light of the advancement in molecular biology and genetics too. In particular, several occupational and environmental exposures—such as trichloroethylene, vinyl chloride, and other organic solvents classified by IARC as group 1 or 2A carcinogens—remain underexplored in this study. For this reason, the potential contribution of specific exposures in high-risk industrial sectors (e.g., painting, automobile, chemical production) represents a valuable future research direction. Third, the GBD "other leukemia" classification is clinically heterogeneous, thus not allowing any consistent metrics forecasting. Finally, while age-standardized rates and ARC estimates offer valuable insights into temporal trends, their interpretation must be made considering the associated uncertainty intervals. Caution is warranted when these intervals cross zero, as this indicates that the observed trend may not be statistically significant—especially for rare leukemia subtypes where data sparsity can amplify uncertainty.

Having a glance at the GBD estimates for leukemia in Italy, we observed a generally encouraging scenario, but not entirely. By examining the crude rate estimates from GBD 2023, it is possible to assess the absolute burden of leukemia and understand how population aging contributes to the observed trends. Unlike age-standardized rates, crude rates reflect the actual number of cases or deaths in the population, capturing the impact of demographic shifts such as an increasing proportion of older individuals: this phenomenon is particularly evident for both AML (huge increase in new cases and death counts), leukemia and CLL (increase in death counts), while ALL and CML showed a net decrease in mortality and DALYs. Regarding GBD 2023 age-standardized estimates, the incidence trend was stable for all subtypes, while the mortality tendency significantly improved for ALL and CML, but worsened for leukemia, CLL and, most of all, for AML: its boost in incidence and mortality represents a serious alarm, even worse among males. In summary, the national burden of leukemia remains severe, but the analysis of the historical series of age-standardized incidence and mortality proved that in the last 30 years Italy was able to partially recover the initial gap both with the GBD Global and High-middle SDI countries, through an updated diagnostic and therapeutic strategy. In this context, future research could incorporate forecasting approaches to anticipate changes in disease burden and support strategic planning. To be effective, such projections should consider evolving clinical practices and demographic trends, and be regularly updated to reflect the rapidly advancing landscape of leukemia research and treatment.

Contributors

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Members of the core research team for this topic area had full access to the underlying data used to generate estimates presented in this article. All other authors had access to and reviewed estimates as part of the research evaluation process, which includes additional stages of formal review.

Data sharing statement

All data used in this study are publicly available through the Global Burden of Disease (GBD) study. The estimates can be accessed and downloaded from the Global Health Data Exchange (GHDx) website: http://ghdx.healthdata.org.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103509.

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