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Survival rates and extra-regional migration patterns of children and adolescents with cancer in Italy: The 30-year experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP) with the Italian hospital-based registry of pediatric cancer (Mod. 1.01)

Andrea Pession[1] | Paola Quarello[2] | Marco Zecca[3] | Maria Luisa Mosso[4] | Roberto Rondelli[5] | Lorenzo Milani[6] | Marisa De Rosa[7] | Tiziana Rosso[4] | Milena Maule[4] | Franca Fagioli[2]

[1]Department of Medical and Surgical Science – Alma Mater Studiorum, Università di Bologna, Bologna, Italy

[2]Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, University of Torino, Torino, Italy

[3]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[4]Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin and A.O.U. Città della Salute e della Scienza di Torino, CPO-Piemonte, Turin, Italy

[5]Department of Pediatrics, IRCCS Azienda Ospedaliero-Universitaria, Bologna, Italy

[6]Centre for Biostatistics, Epidemiology and Public Health (C-BEPH), Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

[7]CINECA – Italian High Perfovrmance Computing Center, Bologna, Italy

Correspondence
Paola Quarello, Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, University of Torino, Piazza Polonia, 94 Torino, Italy.
Email: paola.quarello@unito.it

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Abstract

Since the 1970s, Italian pediatric oncologists have collaborated through the Italian Association for Pediatric Hematology Oncology (AIEOP) network using a common centralized system for the registration of childhood cancer, known as Model 1.01 (Mod. 1.01). In this study, we report on recruitment trends, extra-regional migration and changes in outcome over time in the Italian population of children (0–14 years) and adolescents (15–19 years) registered and treated within the national AIEOP network in the period between 1989 and 2017. In almost 30 years, a cohort of 43,564 patients with a neoplasia diagnosis was registered in Mod. 1.01. The analysis of national extra-regional migration showed that patients tend to migrate from the South to the North and, to a lesser extent, to the Center of the country. During the study period, migration apparently decreased, especially for lymphohematopoietic diseases, whereas it remained substantial for solid tumors. Our data showed a progressive and significant increase in the cumulative survival 5 years after diagnosis since the 1990s, reaching almost 84% for all patients diagnosed in the last decade. Survival rates of Mod. 1.01 patients are similar to those provided by the main national and international reports showing childhood cancer surveillance estimates. The AIEOP Mod 1.01 has proved to be an invaluable tool from both an epidemiological and a health policy point of view, allowing us, in this study, to examine the survival experience of the largest cohort of Italian pediatric cancer patients with a very long follow-up.

KEYWORDS
adolescent, children, epidemiology, registry, survival

Andrea Pession, Paola Quarello, Milena Maule, and Franca Fagioli contributed equally to this study.

What's new?

Reliable and harmonized cancer registration is key for monitoring progress towards tracking all cancer cases within a population and for informing strategic planning and policy-making. Here, the authors describe the largest existing Italian cohort of pediatric and adolescent cancer patients over a period of 30 years by analyzing recruitment trends, extra-regional migration phenomena, and changes in outcome over time. The study illustrates the Italian Association for Pediatric Hematology Oncology (AIEOP)'s hospital registry as a valid tool for contributing to epidemiological research and for monitoring and improving the survival of children and adolescents with cancer in Italy.

1 | INTRODUCTION

Approximately 1500 children (0–14 years) and 900 adolescents (15–19 years) are diagnosed with cancer every year in Italy and more than 44,000 people living in Italy have had a cancer diagnosis during childhood.[1–3] Over the last 3–4 decades, the survival rates of children with cancer have greatly improved, thanks to the improvements in diagnostic tools, risk-adapted therapeutic strategies, and development of national and international collaborative groups.[4–7]

Since the 1970s, the Italian pediatric oncologists have collaborated through the Italian Association for Pediatric Hematology and Oncology (AIEOP) network that includes 49 centers, all part of the Italian National Health System, dedicated to the treatment of children and adolescents with oncologic or hematologic diseases.[8] Although characterized by different volumes of activity and specificities, all AIEOP centers cooperate with each other, adopting shared diagnostic procedures and treatment protocols.

This approach serves the dual purpose of offering the best possible care to every patient close to his/her home, avoiding pointless migrations, wherever possible and, at the same time, providing diagnostic procedures or treatments that are too complex to be administered in every local hospital, such as a second pathologic review, specific molecular analyses, surgical procedures demanding specific expertise, and early-phase clinical trials.

In this context, reliable cancer registration and the collection of harmonized health information is key for monitoring the progress towards the goal of identifying all cases within a population and to inform policy makers about priority setting and decision planning. Since 1989, AIEOP network centers have adopted a common centralized system for the registration of childhood cancer, known as Model 1.01 (Mod. 1.01 hereafter), with the main aim of setting up a hospital-based national Registry of Pediatric Cancer.[8,9]

The strength of Mod. 1.01 is that it is a patient-centered model, which includes two separate sections, one containing the patient's personal data and the other data on the management of the first diagnosis: transfer to/from other centers, any second malignancy, and follow-up update without any duplication of information. Recently, AIEOP conceived a central diagnosis review (CDR) platform linked to Mod. 1.01. At diagnosis, the patient is assigned to the CDR platform and referred to a given centralized laboratory depending on his/her primary diagnosis, according to the AIEOP referral centers and the biologists/pathologists specialized in each type/family of cancer. The CDR platform allows the pathologists to return their report to the clinicians in charge of the patient, and have it linked to the other patient's records available in Mod. 1.01.[10]

Furthermore, all AIEOP centers deliver a digital document containing diagnosis and treatment data to all cancer patient survivors (survivorship passport), with personalized recommendations according to the most recent international guidelines published by the International Guidelines Harmonization Group and PanCareSurFup, in order to monitor and prevent late effects.[11] This project was developed in collaboration with the European Society of Pediatric Oncology (SIOPE), and thanks to the AIEOP platform, Italy has been the first European country to adopt this tool, aimed at improving patients' quality of life.

The main purposes of registering childhood tumors are to contribute to etiological research and to study survival rates. Since childhood tumors are treatable but very difficult to prevent, estimating survival, which also involves long-term follow-up planning to monitor late effects and potential recurrences, is crucial. Globally, high-quality data on the incidence of cancer are available only in one in three countries and, on mortality, in one in four.[12] The situation is even more critical for childhood cancers. In a recent editorial, Ilbawi et al. commented on serious deficiencies in childhood cancer registration in 22 Eastern Mediterranean countries concluding that weak cancer registries limit appropriate service planning and negatively impact monitoring of quality of care and treatment progress.[13,14]

Here we describe the largest existing cohort of Italian pediatric and adolescent cancer patients over a 30-year period by analyzing recruitment trends, extra-regional migration phenomena, and changes in outcome over time. The aim of this study is to illustrate the AIEOP Mod. 1.01 hospital registry as a valid tool to contribute to epidemiological research and consequently to the improvement in survival of children and adolescent cancer patients in Italy.

2 | MATERIALS AND METHODS

2.1 | The dataset

From 1989, all centers in the AIEOP network started registering all children and adolescents with oncologic or hematologic diseases or

immunodeficiencies. Data on demographic characteristics (gender, town and date of birth, town of residence at diagnosis) and clinical features (date of diagnosis, cancer site, morphology and stage, center where the diagnosis was made and therapy implemented) were collected. Data collection was performed through a specifically designed form (Mod. 1.01) and filed centrally in a dataset at the AIEOP Operational Office in Bologna, where properly trained clerical staff verify information validity. All diagnoses were classified according to the International Classification of Childhood Cancer-3 (ICCC-3).[15] The registration form, originally paper-based, was replaced in 2000 with an electronic version on a platform managed by the computing center of the Italian Inter-University Consortium (CINECA). It was thus adopted by all AIEOP centers through the official AIEOP website (www.aieop.org) as a registration form for each patient with a tumor diagnosis or treated in any AIEOP center, whether or not registered in any official protocol.

This system is based on advanced technological infrastructure which allows the implementation of dedicated web-based platforms, such as those used to conduct clinical studies.

The dataset is maintained according to the criteria for Advanced Multicenter Research and Security in collaboration with CINECA, Bologna. CINECA's IT infrastructure is certified for data quality procedures (ISO 27001:2013 certification, https://www.cineca.it/en/content/certifications) and through hypertext transfer and secure sockets layer protocol encryption standards. The AIEOP platform provides a secure online database that guarantees compliance with an up-to-date high security and quality standard and meets all the requirements set by the European General Data Protection Regulation. A total of 49 clinical units dedicated to treating children and adolescents with cancer operate throughout the country. Today, several databases (Mod. 1.01, Hematopoietic Stem Cell Transplant (HSCT) Registry, and 10 disease-oriented databases) have been set up. All these databases are structured in a hierarchical-relational way, providing for a patient-oriented table containing registration data, patient's diagnosis, treatment, side effects, follow-up (and death), and any possible information regarding the patient's transfer to another center. The follow-up table includes a general section, common to all AIEOP databases, and a specific section for each disease.

2.2 | Ascertainment of vital status

For this study, the vital status (i.e., whether alive, dead or lost at the closing date of follow-up) was obtained from the Vital Statistics Office of the towns of residence using an ad hoc request form from the Cancer Epidemiology Unit of the University of Torino. If not available, the vital status recorded in the dataset by AIEOP Centers was considered. Follow-up and vital status were defined, as of 2017, for all subjects.

2.3 | Statistical analysis

Time trends of annual recruitments of patients in Mod. 1.01 were estimated using Poisson regression analysis and presented as the annual percent change (APC) with 95% confidence interval.

All AIEOP centers were ranked according to their volume of activity (number of patients enrolled during the study period) and divided into three groups defined as low (less than 20 patients/year on average), medium (between 20 and 50 patients/year on average), and high (more than 50 patients/year on average). Recruitments were analyzed by disease type (neoplastic and non-neoplastic), age groups (0, 1–4, 5–9, 10–14, and 15–19 years of age), geographical macro-area (North, Center, South and Islands), volume of activity (high, medium or low) of the center, tumor type (ICCC-3 groups), and tumor groups (lympho-hematopoietic neoplasms [LLs] and solid tumors [STs]). The pattern of migration of patients from their area of residence to the site of care was estimated by means of the proportion of patients that were treated in a geographical macro-area different from that in which they reside, and the agreement between the macro-areas of family residence and that of the AIEOP center where the therapy program was implemented was estimated through the weighted Cohen's kappa coefficient,[16,17] overall and by decade of diagnosis. The weights were assigned in such a way that greater movement led to less concordance.

Cumulative survival percentages were estimated using the Kaplan and Meier method[18] for all major types of childhood cancer according to 5-year periods of diagnosis, gender, age class (0, 1–4, 5–9, 10–14, 15–19 years) at diagnosis, volume of activity (high, medium or low) of the center, geographical macro-area (North, Center, South and Islands), type of treatment (according to national or international protocol or following local guidelines). Cumulative survival curves were compared through the log-rank statistic for homogeneity and temporal trends.[19] Survivals were analyzed by comparing the 5-year observed cumulative survival by gender, age class and type of treatment in three subsequent 10-year periods of diagnosis.

Statistical analysis was performed using Stata[20] and R[21] softwares.

3 | RESULTS

The total number of cases recorded by all AIEOP centers until August 4, 2017 and at 0–19 age, was 54,610, 5711 of which were diagnosed before 1989. Eighty-nine percent (43,564/48,899) of all registered patients were affected by oncologic diseases and the remaining 11% (5335/48899) by hematological non-oncological diseases or primary immunodeficiencies. The distribution of oncological cases included in this analysis by gender, period of diagnosis, age groups and ICCC-3 groups are shown in Supplementary Table 1.

The annual recruitment and corresponding trends of the 43,564 cancer cases registered in the 29 years of the study period, from 1989 to 2017, is shown overall in Supplementary Figure 1, and by age groups in Supplementary Figure 2.

3.1 | National extra-regional migration

We examined the distribution of patients by macro-area of residence at diagnosis and by location of the AIEOP clinical units where

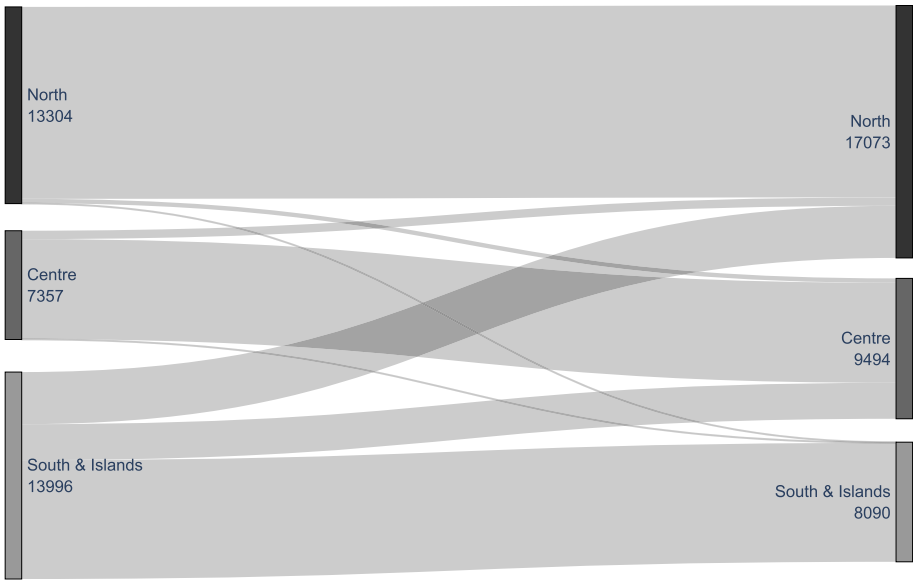


FIGURE 1 Pattern of migration of all patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 1989 and 2017. On the left-hand side, the number of patients is shown by geographical macro-area of residence (North, Center, South, and Islands), on the right-hand side the number of patients is shown by geographical macro-area of treatment. [Color figure can be viewed at wileyonlinelibrary.com]

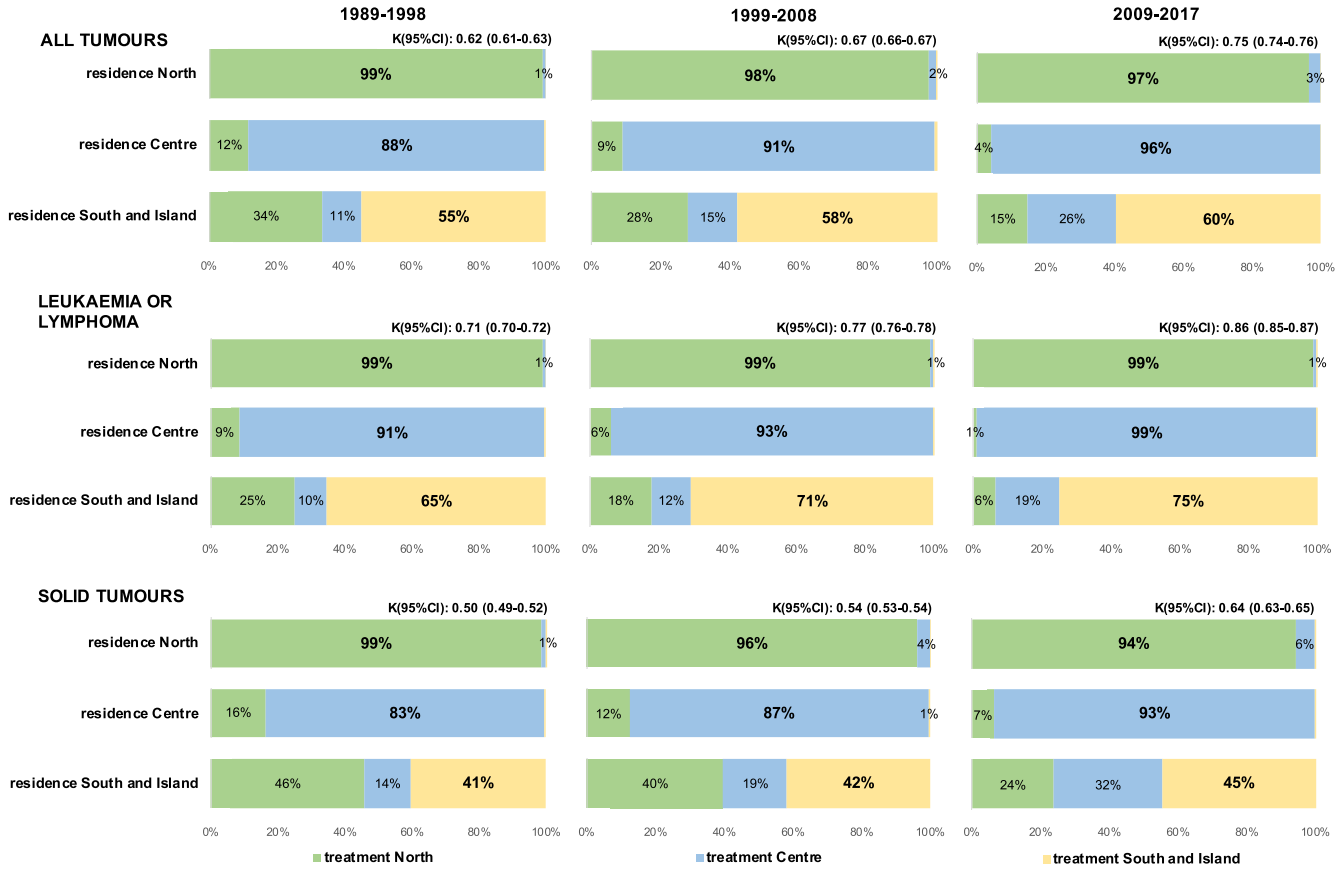


FIGURE 2 Pattern of migration of all patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 1989 and 2017, by three subsequent 10-year periods of diagnosis (1989–1998, 1999–2008, 2009–2017). The proportions of patients residing in each geographical macro-area (North, Center, South, and Islands) are shown by macro-area of treatment. The weighted Cohen's kappa coefficients calculated between residence and AIEOP center location areas are shown with 95% CI.

treatment was performed. Figure 1 shows the overall pattern of migration of children and adolescents throughout the whole study period (1989–2017).

Figure 2 shows the proportions of patients residing in each geographical macro-area (North, Center, South, and Islands) migrating in a different macro-area to be treated in three subsequent 10-year

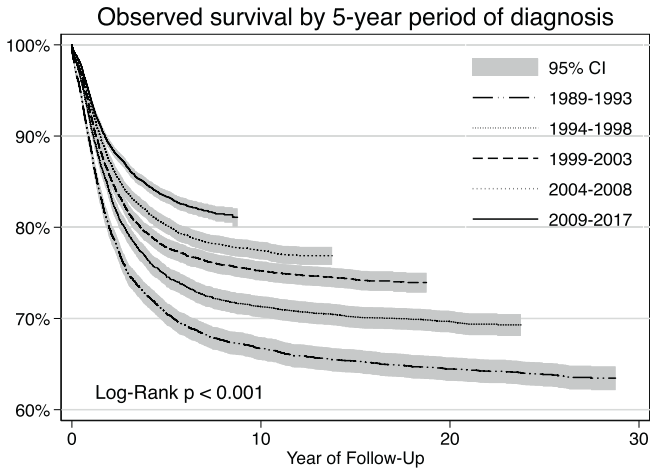


FIGURE 3 Observed cumulative survival (Kaplan Meier) and 95% CI of all patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 1989 and 2017 up to 10 years of follow-up, by 5-year period of diagnosis: 1989–1993, 1994–1998, 1999–2003, 2004–2008, 2009–2017 (the duration of the last period of diagnosis is 9 years).

periods of diagnosis (1989–1998, 1999–2008, 2009–2017). The weighted Cohen's kappa coefficients calculated between residence and AIEOP center location areas are shown with 95% confidence intervals (CIs). Overall, patients tend to migrate from the South to the North and, to a lesser extent, to the Center of the country. Migration from the Center to the North is much more contained. Over the three periods analyzed, migration apparently decreased, especially for lymphohematopoietic diseases, as also shown by the increasing agreement index, going from 0·62 (95% CI, 0·61–0·63) in 1989–1988 to 0·75 (95% CI, 0·74–0·76) in 2009–2017 for all tumor types and from 0·71 (95% CI, 0·70–0·72) to 0·86 (95% IC, 0·85–0·87) for LL. On the opposite, migration from the South remained somewhat higher for ST (0·64, 95% IC, 0·63–0·65).

3.2 | Survival analysis

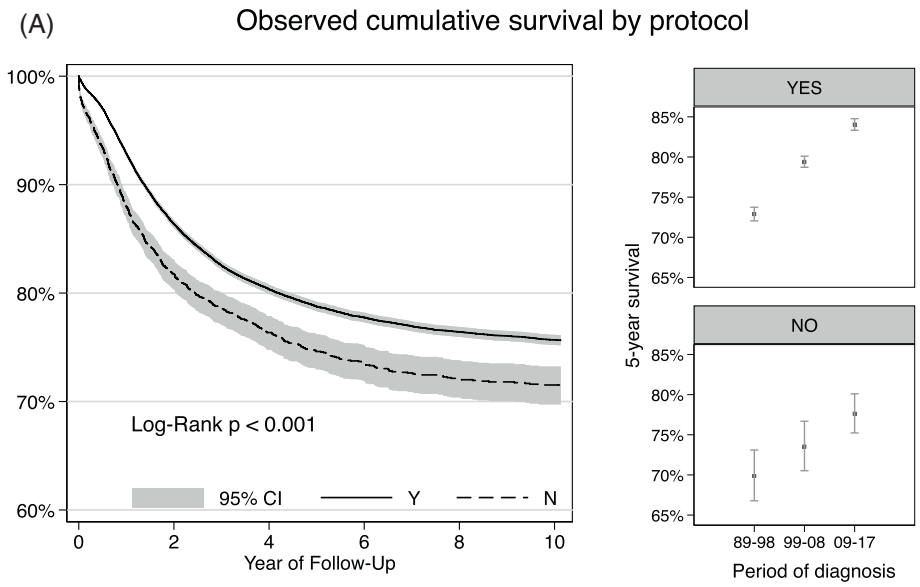
Median follow-up time for cases was 20·5, 11·6, and 3·6 years for those diagnosed in 1989–1998, 1999–2008, and 2009–2017, respectively. Children lost to follow-up and for whom no information was retrieved from vital office registrars or treatment centers were 1686, of whom 364 migrated abroad, 1085 were not found and 237 were lost to follow-up.

Cumulative observed survival for all tumor types and children of all ages (0–19 years) is shown by means of Kaplan Meier curves and 95% CIs in Figure 3 according to four 5-year (1989–1993, 1994–1998, 1999–2003, 2004–2008) and one 9-year (2009–2017) periods of diagnosis. The overall cumulative survival 5 years after diagnosis, has been increasing since the 1990s, from 71%, (95% CI, 69–72) for patients diagnosed in 1989–1993 to 84% (95% CI, 83–84) for patients diagnosed in 2009–2017 (p-value of the log-rank test <.001).

Figure 4 and Supplementary Figures 3–4 show the cumulative observed survival for all tumor types and children of all ages (0–19 years) by means of Kaplan Meier curves up to 10 years of follow-up, by sex, age class (0, 1–4, 5–9, 10–14, and 15–19), type of treatment (according to national or international protocol or following local guidelines), and volume of activity of the treating center. Shaded areas around survival curves represent 95% CI and are not shown for age classes to improve readability because they partially overlap. Five-year survival proportions are also shown for two 10-year and one 9-year periods of diagnosis (1989–1998, 1999–2008, 2009–2017), separately for females and males, for each age class and type of treatment. Survival has greatly improved across all variables (sex, age, and type of treatment) considered in the period under study, as also shown by Supplementary Table 2, that shows the observed 5-year survival of all patients (ages 0–19) and for children (ages 0–14) by ICCC main groups and selected subgroups, and by period of diagnosis (1989–1993, 1994–1998, 1999–2003, 2004–2008, 2009–2017).

Girls have slightly better survival than boys, with 5-year proportions of survivors reaching 84% (95% CI, 83–85) and 83% (95% CI, 82–84), respectively, for patients diagnosed in 2009–2017 (Supplementary Figure 3). Children in their first year of age exhibit the steepest decline immediately after diagnosis but the curve flattens out quite quickly and survival becomes higher than that of the other age groups after 4 years following diagnosis, with the 5-year survival reaching 84% (95% CI, 82–87) for the most recent period of diagnosis. For the other age classes, long term survival decreases with increasing age, with similar figures for patients 10–14 and 15–19 years old (Supplementary Figure 4). The cumulative survival is higher for patients enrolled in a national or international clinical trial (5-year survival for patients diagnosed in 2009–2017: 84%, 95% CI, 83–85) than for those treated following local protocols: 78%, 95% CI, 75–80, but survival has improved in time for both groups of patients (Figure 4A). The larger uncertainty of survival estimates for patients treated according to local guidelines is due to the much smaller number of patients in this group. Survival increases with decreasing volume of activity of the treating center: high volume 82%, 95% CI, 81–83, low volume 87%, 95% CI, 85–88 (Figure 4B) for patients diagnosed in 2009–2017.

Cumulative survival was also estimated by the geographical macro-area in which the therapy program was implemented and the geographical macro-area of residence of the patients (Figure 5). This analysis was restricted to the most recent period of diagnosis (2009–2017) to account for the downward trend in patient migration and to include the most recently established AIEOP centers. Cumulative survival by area of treatment showed better survival for children and adolescents treated in the South and Island (5-year survival: 86%, 95% CI, 85–88) than in the Center (84%, 95% CI, 82–85) and in the North of the country (82%, 95% CI, 81–83). This finding should be interpreted in the light of the geographical distribution of the largest referral centers, mostly located in the North and Center of the country, and is consistent with the findings relative to survival by volume of activity of the treating centers. When survival was examined by



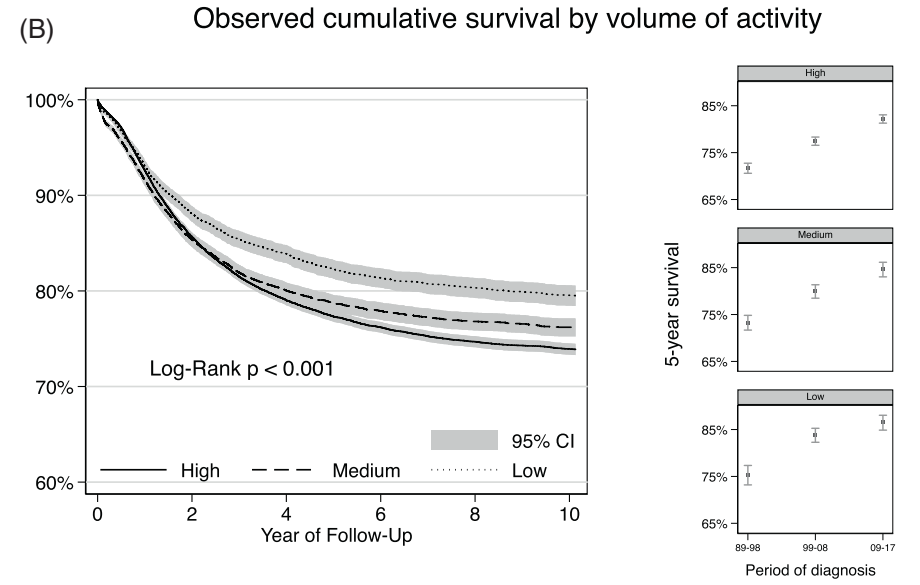


FIGURE 4 (A) Observed cumulative survival and 95% CI of all patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 1989 and 2017, by type of treatment (according to national or international protocol or following local guidelines). On the left: Kaplan Meier curves and 95% CI (shaded area) up to 10 years of follow-up. On the right: 5-year observed survival and 95% CI (bars) for 10- and 9-years periods of diagnosis (1989–1998, 1999–2008, 2009–2017), separately for patients treated according to standard protocol (Y) or local guidelines (N). (B) Observed cumulative survival and 95% CI of all patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 1989 and 2017, by volume of activity of the treating center (Low: less than 20 patients/year; Medium: between 20 and 50 patients/year; High: more than 50 patients/year). On the left: Kaplan Meier curves and 95% CI (shaded area) up to 10 years of follow-up. On the right: 5-year observed survival and 95% CI (bars) for 10- and 9-years periods of diagnosis (1989–1998, 1999–2008, 2009–2017), separately for high, medium, and low activity volume.

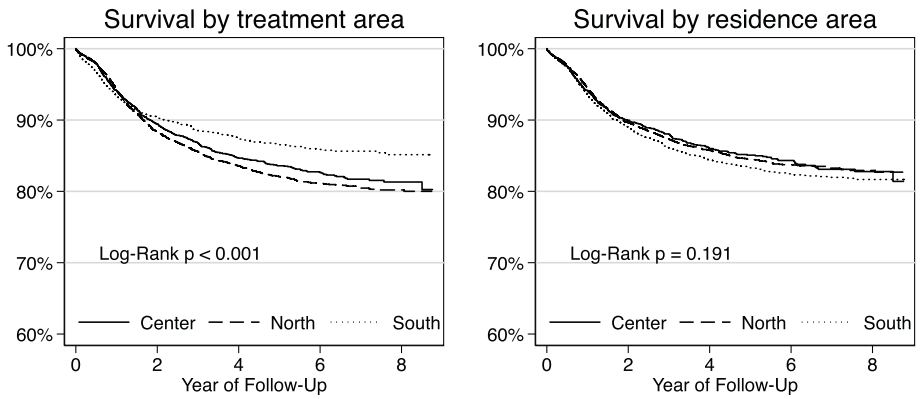


FIGURE 5 Observed cumulative survival of patients (0–19 years old) registered by Mod. 1.01 in all Italian AIEOP centers between 2009 and 2017, by geographical macro-area of treatment (left) and macro-area of residence (right). Confidence intervals shaded areas are not shown to improve readability.

macroarea of residence of patients, no differences were observed between survival in the 3 geographical macro-areas (*p*-value for the log-rank test .191). Consistently, no differences were observed if the analyses were restricted to patients residing and being treated in the same macro-area (Supplementary Figure 5, *p*-value for the log-rank test .216).

TABLE 1 Five-year survival of children with cancer as reported by national and international population- and hospital-based cancer registries in similar calendar periods for all cancer types and for the most common ICCC groups, including Mod. 1.01 of the AIEOP network.

			0-14 years five-years survival estimates and 95% confidence intervals											
				Leukemia			Lymphoma				Malignant CNS			
Registry name	Country	Period	All cancer types	I Leukaemia	Ia Lymphoid leukaemia	Ib Acute myeloid leukaemia	II Lymphoma	IIa Hodgkin lymphoma	IIb Non Hodgkin lymphoma	IIc Burkitt lymphoma	III Malignant CNS	IIIa Ependymomas	IIIb Astrocytomas	IIIc Intracranial
AIEOP[a]	**Italy**	**2009–2017**	**84% (83–85)**	**85% (84–86)**	**88% (87–89)**	**74% (71–78)**	**94% (93–96)**	**96% (95–98)**	**93% (90–95)**		**76% (74–78)**	**84% (78–90)**	**84% (81–87)**	**65% (59–69)**
AIRTUM (a)	Italy	2003–2008	82% (80–83)	85% (83–87)	89% (86–91)	65% (56–73)	89% (86–92)	94% (90–97)	84% (79–89)		64% (59–68)	-	-	62% (53–70)
EUROCARE (b)[b]	Europe	2000–2007	78% (77–78)	-	86% (86–87)	63% (61–65)	-	95% (94–97)	84% (82–86)	90% (89–92)	58% (56–59)	63% (58–67)	62% (59–64)	57% (55–60)
NRCT (c)	UK	2001–2005	78%	83%	88%	64%	88%	95%	83%		71%	67%	81%	56%
SEER (d)[b]	USA	2001–2007	84% (whites)	86%	91%	64%	-	96%	86%	-	75%	-	-	-
REETI-SEHOP (e)[a]	Spain	2005–2009	77% (76–78)	79% (76–81)	83% (81–85)	62% (55–68)	88% (86–91)	96% (93–99)	85% (81–88)[c]		67% (64–70)	65% (56–73)	80% (76–84)	53% (47–60)
		2010–2014	81% (80–82)	83% (81–85)	86% (84–87)	69% (63–75)	94% (92–96)	98% (95–100)	92% (89–95)[c]		72% (69–74)	75% (67–82)	86% (82–89)	50% (45–56)
ACCR (f)[b]	Australia	2007–2016	86% (85–87)	-	93% (92–94)	77% (72–81)	-	-	90% (86–94)	93% (87–97)	-	77% (70–83)	85% (82–88)	61% (55–66)
Cancer Research (g)	UK	2009	82% (80–84)	-	-	-	-	-	-	-	-	-	-	-
		2017	85% (84–86)	-	-	-	-	-	-	-	-	-	-	-

Source: (a) AIRTUM (Italy), Epidemiol Prev. 2013 Jan-Feb;37(1 Suppl 1):1-225; (b) EUROCARE (Europe), https://www.eurocare.it/LinkClick.aspx?fileticket=hcgmq6vAq6Y%3d&tabid=61; (c) NRCT (UK), https://www.ccrg.ox.ac.uk/datasets/survivalrates.shtml; (d) SEER (USA), https://seer.cancer.gov/archive/csr/1975_2008/results_merged/sect_28_childhood_cancer.pdf; (e) RETI-SEHOP (Spain), https://www.uv.es/mti/pdfs/Informe_RETI-SEHOP_1980-2020.pdf; (f) ACCR (Australia), https://cancerqld.org.au/research/queensland-cancer-statistics/accr/; (g) Cancer Research (UK), https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/childhoodcancersurvivalinengland.

[a]Clinical registry.

[b]Relative survival.

[c]Includes types IIb, IIc, and IIe.

Survival of patients enrolled in the Mod. 1.01 are better understood if they are examined in a more general context. Table 1 shows 5-year survival of children with cancer as reported by national and international population- and hospital-based cancer registries, including Mod 1.01, in calendar periods similar or partially overlapping with the most recent period of diagnosis analyzed in our study (2009–2017). Survival figures are shown for all cancer types and for the most common ICCC groups. In some reports, similarly to our study, the absolute cumulative survival is reported, whereas in others relative survival is shown. Since children generally have extremely low mortality rates from other causes compared to adults, the impact of non-cancer mortality on relative survival may be minimal, making relative survival rates similar to absolute survival rates.

4 | DISCUSSION

In this study, we report on cancer enrolment trends and survival rates in the Italian population of children (0–14 years) and adolescents (15–19 years) registered and treated within the national AIEOP network in the period 1989 and 2017 using data from the AIEOP hospital-based registry (Mod. 1.01).[8] In almost 30 years, a very large cohort of 43,564 patients with a neoplasia diagnosis at age 0–19 years was recruited. The coverage of the present database was considerably high both in the North, Center and South of Italy. Since there is no pediatric onco–hematology unit in Italy that is not affiliated to the AIEOP, data included in this clinical database can be considered exhaustive and representative of the whole of Italy. This study confirms the importance and usefulness of a clinical registry of childhood cancer which is rich in clinical information and allows evaluation of treatment protocols and monitoring of outcomes.

In Italy, a solid collaboration between the national hospital-based registry (AIEOP mod 1.01) and the Italian network of population-based cancer registries (AIRTUM) ensures an exhaustive coverage of the whole country. Initiatives to facilitate data exchange and collaboration between institutions could and should be endorsed to guarantee the availability of high-quality and timely data on the incidence of childhood cancer and patients' survival. New international partnerships to facilitate data flow are emerging such as ChildGICR (part of the Global Initiative for Cancer Registry Development) project.[22] Countries joining this initiative are supported in the implementation of childhood cancer registries by initiating education, implementation and research strategies, engaging community-based networks according to the profile and registration situation of each country.

The enrolment rate for children and adolescents in the AIEOP Mod. 1.01 database has increased over the 30-year period analyzed in this study, as shown by an average annual percent increase of +2.7% (95% CI, 2.5–2.7). This trend mainly reflects the continuously improving ability of centers to enroll and treat children and adolescents with cancer rather than the underlying incidence time trends.[23,24]

In particular, we found that the increase in recruitment is more than 4 times higher in adolescents than in children. Adolescents with cancer form a subgroup of patients whose clinical management and access to the best possible treatment remain challenging, especially when compared with improvements related to the children's care model achieved over the years.[25,26] A recent Italian national study has shown that the percentage of adolescents treated at AIEOP centers has increased over the years, with an Observed/Expected (O/E) ratio rising from 0.1 in 1989–2006 to 0.37 in 2013–2017.[27] Several reasons may explain different trends between adolescents and children. In the past, the upper age limit for admission to AIEOP pediatric oncology units, set at 14–16 years, was seen as one of the reasons why the AIEOP network was much less effective in serving adolescents than children. Over the last decade, this scenario has changed, and the upper age limit is no longer an obstacle to the inclusion of adolescents. Moreover, several initiatives were taken to raise awareness in the scientific community to encourage the implementation of specific programs for adolescent cancer patients.[27,28]

The intra-national migrations of patients to AIEOP centers located even very far from their residence reflects the complex interplay between healthcare accessibility and regional disparities. The need for families with children with cancer to migrate within their own nation to access adequate care sheds light on the uneven distribution of medical resources in Italy. Analyzing patterns of patient migration provides useful information and can highlight areas in which the network of AIEOP centers could be strengthened.[17,29]

In our study, we found that patients tend to migrate from the South to the North and, to a lesser extent, to the Center of the country to receive treatment. Migration from the Center to the North is much more contained. This may partly reflect the larger number of AIEOP centers in the North of Italy and their longer history.

Migration is more pronounced for patients with ST probably due to referral to selected centers located in the North and the Center providing treatments that are too complex to be administered in every center (such as radiotherapy, and surgical procedures demanding specific expertise like neurosurgery). Remarkably, the migration phenomenon decreased over the study period, especially for LL and, to a lesser extent, also for ST. This may reflect the continuous efforts to support all clinical units and to enhance centralized services which all centers can benefit from, even when not locally available. This strategy has been envisaged to ensure optimal cancer-directed therapy and the best quality of care at a reasonable distance from the family home, thus reducing the social impact and costs of the disease.

In this context, an important organizational feature developed by AIEOP over the years is a centralized review process for all oncological diagnosis. Correct histologic and molecular diagnosis can be challenging for rare and heterogeneous disease like pediatric tumors.[30,31] The AIEOP network includes reference laboratories with proven and demonstrable experience to which tumor samples can be submitted for a final confirmatory diagnosis by all AIEOP treatment centers ensuring the best diagnostic accuracy and preventing inappropriate therapy protocols (both over- and under-treatment). Noteworthy, through the integration of reviewed histopathologic diagnosis into comprehensive clinical patient data, AIEOP also aims to improve the quality of data itself.[31]

The survival of pediatric and adolescent patients with cancer has substantially increased in recent decades.[7] In this scenario, efforts to improve every single stage of cancer cure have become increasingly significant. Our data showed a progressive and remarkable increase in cumulative survival at 5 years after diagnosis since the 1990s.

Survival rates of AIEOP Mod. 1.01 patients are similar to those reported in overlapping periods by the main national and international childhood cancer surveillance programs (Table 1). For specific ICCC groups, such as malignant tumors of the central nervous system, especially ependymomas and embryonal tumors and some lymphohematopoietic diseases, such as acute myeloid leukemia and non-Hodgkin lymphoma, we observed slightly higher survival rates. Differences are more pronounced in comparison with population-based cancer registries, such as the US SEER or the registries contributing data to the EUROCARE study. This is not unexpected and should be interpreted in the context of the registries' characteristics, such as the completeness of case ascertainment of population-based registration and the possibility of selection bias in hospital-based registration. On the other hand, considering that Italy has had a universal public healthcare system since 1978 and treatment of pediatric—as well as adult—cancer is completely free of charge and based on public hospitals, we may exclude biases due to selection on socio-economic background.

When the volume of activity and the geographical macro-area of treatment were considered, overall survival was higher in patients treated in centers with low volume of activity and in centers located in Southern Italy. This result may seem counterintuitive at first sight, but it should be interpreted in the light of the geographical distribution of the largest referral centers, which are mostly located in the North and Center of the country and is consistent with the fact that the migration of patients from the South mainly involves patients with worse prognosis who are referred to the largest and specialized referral centers. Geographical differences in survival were indeed drastically reduced when the survival curves were examined by patients' macroarea of residence (Figure 5) or when the analyses were restricted to patients residing and being treated in the same macroarea (Supplementary Figure 5).

The increase in survival over the past 30 years has been attributed to advances in treatment and supportive care driven by clinical research efforts. Collaborative international and national pediatric clinical trials have been instrumental in driving this improvement.[32] In our study, survival of children and adolescents with cancer was significantly higher in patients treated according to international and national standard protocols in comparison with those treated according to therapeutic strategies designed locally, who represent a small group of patients whose numbers are steadily decreasing. Our results confirm that enrolment into protocols is fundamental to improve clinical outcomes for cancer patients.

One of the major strengths of this study is the size and national coverage of the largest cohort of Italian pediatric patients with cancer with long term follow-up. The inclusion of the 15–19 age group and the ICCC-3 tumor classification allow international comparison which is essential for etiological research and effective health policies and protocols. In a framework of universal and free of charge health system, the AIEOP network and its patient-centered model provide the opportunity to deliver optimal cancer management with centralized diagnosis, enrolment into clinical trials and personalized long term follow-up, avoiding disparities due to geographical issues or socio-economic determinants. Among the limitations of our study, we acknowledge that we have no information on patients who were not referred to pediatric centers. This bias may be partly corrected by raising awareness of data collection among professionals such as neurosurgeons who treated patients with specific tumor subtypes as low-grade CNS which do not require additional treatment to surgery and thus are often not referred to pediatric centers. Another important point is the need to work closely with adult oncologists who may be treating adolescent patients with oncological diseases.

In conclusion, the AIEOP Mod. 1.01 proved to be an invaluable tool from both an epidemiological and a health policy point of view. The analyses of the collected data allow AIEOP to support improvement actions, some of which have been active for a while, such as the increase of the upper age limit for admission to AIEOP centers. Other initiatives are in the process of being defined, such as the creation of a joint Italian pediatric tumor registry in collaboration with AIRTUM to assess access to pediatric oncological services in the national territory and to monitor the incidence of childhood neoplasms in a timely manner for the purposes of etiological research. Other strategies are still being envisaged, such as those aimed at responding to the new needs of the pediatric cancer population in Italy, which is destined to become increasingly multiracial and multi-ethnic in the coming years. These are just some of the many challenges that remain open in the field of pediatric onco-hematology and that the network of AIEOP centers is called upon to address in the near future.

AUTHOR CONTRIBUTIONS

Andrea Pession: Conceptualization; validation; writing – original draft. **Paola Quarello:** Conceptualization; data curation; validation; writing – original draft; writing – review and editing. **Marco Zecca:** Data curation; validation; writing – review and editing. **Maria Luisa Mosso:** Data curation; investigation; validation; writing – review and editing. **Roberto Rondelli:** Data curation; investigation; validation; writing – review and editing. **Lorenzo Milani:** Data curation; formal analysis; validation; writing – review and editing. **Marisa De Rosa:** Data curation; investigation; writing – review and editing. **Tiziana Rosso:** Data curation; formal analysis; writing – review and editing. **Milena Maule:** Conceptualization; data curation; formal analysis; methodology; writing – review and editing. **Franca Fagioli:** Conceptualization; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

In 2013, Mod. 1.01 was approved as a "retrospective and prospective observational study protocol on subjects enrolled at AIEOP centers" by Sant' Orsola Malpighi Hospital Ethics Committee, Bologna, Italy (3637/2013).

ORCID

Paola Quarello https://orcid.org/0000-0002-1940-7375

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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