P399

Outcome Predictors for Patients Aged 55 Years and Older With Acute Lymphoblastic Leukemia: A Retrospective Study From The HARMONY Big Data Platform

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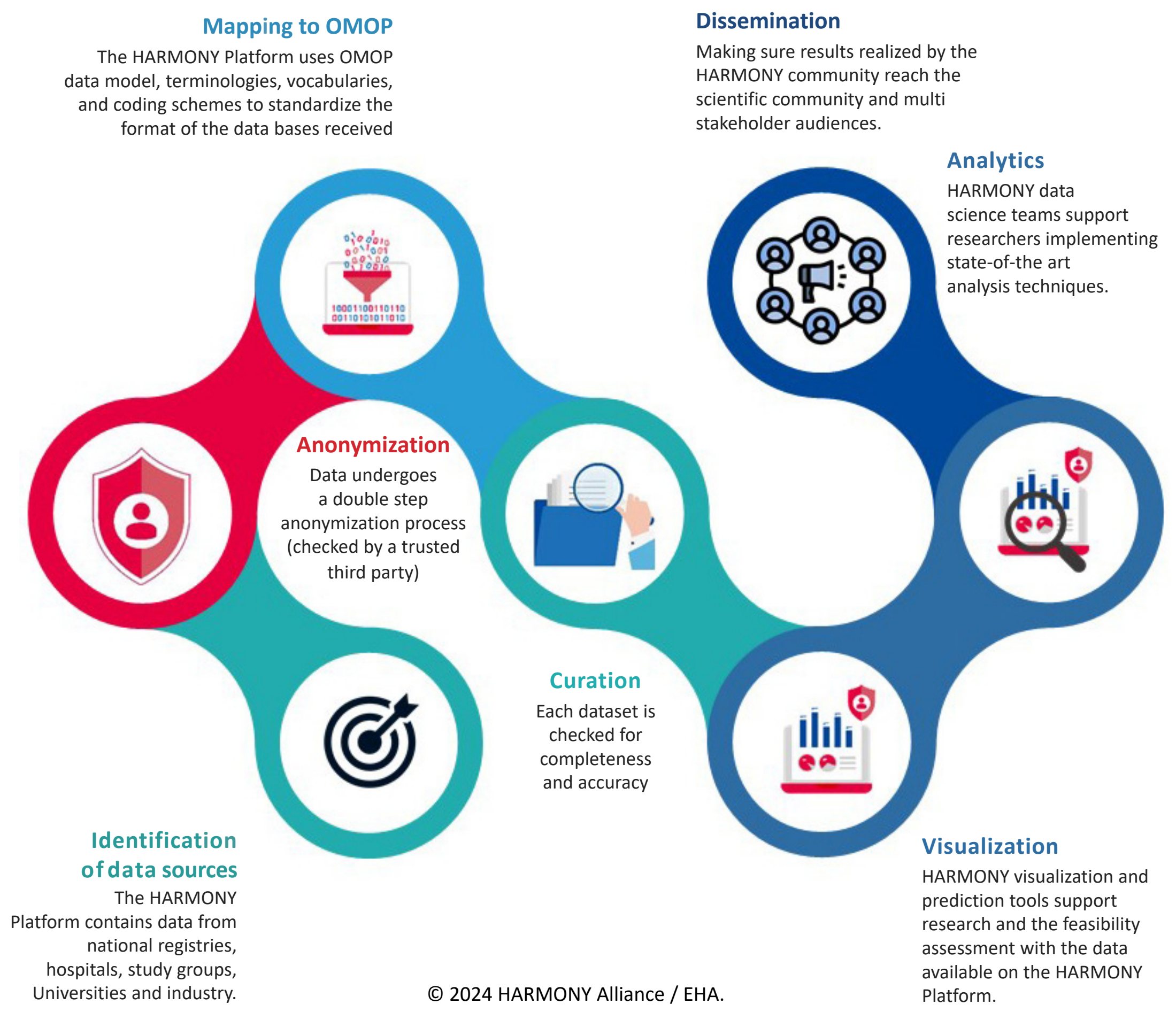
BACKGROUND

- A minority of patients with acute lymphoblastic leukemia (ALL) are diagnosed aged ≥55 years[1,2]
- Outcomes for older adults with ALL have been poor, with a historical 5-year overall survival (OS) rate of ~20%[2,3]
- The HARMONY Alliance is a large, multinational public-private partnership gathering data on hematologic cancers maintained in several individual databases from European clinical trials and registries (**Figure 1**)[4]

Figure 1: The HARMONY data processing pipeline



Mapping to OMOP
The HARMONY Platform uses OMOP data model, terminologies, vocabularies, and coding schemes to standardize the format of the data bases received

Dissemination
Making sure results realized by the HARMONY community reach the scientific community and multi stakeholder audiences.

Analytics
HARMONY data science teams support researchers implementing state-of-the art analysis techniques.

Anonymization
Data undergoes a double step anonymization process (checked by a trusted third party)

Curation
Each dataset is checked for completeness and accuracy

Identification of data sources
The HARMONY Platform contains data from national registries, hospitals, study groups, Universities and industry.

Visualization
HARMONY visualization and prediction tools support research and the feasibility assessment with the data available on the HARMONY Platform.

OBJECTIVES

- To identify predictors of clinical outcomes for patients aged ≥55 years with ALL using the HARMONY big data platform

METHODS

- This retrospective cohort study used HARMONY data from 1995 to 2020
- The database utilizes the Observational Medical Outcomes Partnership (OMOP) Common Data Model. Patients were identified via the appropriate OMOP codes
- Patients aged ≥55 years with confirmed B-cell ALL at diagnosis were included
- To account for patients selected for allogeneic hematopoietic stem cell transplantation (HSCT), a landmark analysis was performed; the Simon–Makuch estimator and the "clock-back" methods[5] were used to evaluate OS before and after HSCT to better account for HSCT waiting list time
  - The "clock-back" method rests on the less restrictive semi-Markov assumption that the time spent on the waiting list does not affect post-HSCT mortality and adjusts death/censoring times by subtracting waiting time for HSCT
- Univariate and multivariate analyses were performed to identify predictors of survival and response outcomes

RESULTS

Patients

- This cohort includes 266 patients aged ≥55 years diagnosed with B-cell ALL between 1995 and 2020 (**Supplementary Figure 1**)
- Patient demographics and disease characteristics are shown in **Table 1**
- In the 3 months following diagnosis, 155 patients (58.3%) received chemotherapy, 86 (32.3%) received a tyrosine kinase inhibitor (TKI), 22 (8.3%) received immunotherapy, and 46 (17.3%) had no treatment recorded
- After ALL diagnosis, 38 patients (14.3%) received HSCT; 34 of 38 (89.5%) did so within 1 year of diagnosis

Table 1: Patient demographics and disease characteristics at ALL diagnosis

	N=266
Age at ALL diagnosis[a], median (range), y	61.0 (55.0–83.0)
Age group, n (%)	
55–59	109 (41.0)
60–64	70 (26.3)
65–69	46 (17.3)
70–74	30 (11.3)
≥75	11 (4.1)
Sex, n (%)	
Male	133 (50.0)
Female	133 (50.0)
Cytogenetic risk, n (%)	n=264
Poor	132 (50.0)
Intermediate	125 (47.3)
Good	7 (2.7)
Ph, n (%)	n=214
Ph+	113 (52.8)
Ph-	101 (47.2)
ECOG PS as observed, n (%)	n=190
≤ Grade 2	177 (93.2)
≤ Grade 1	156 (82.1)
> Grade 1	34 (17.9)
WBC count, median (interquartile range), ×10⁹/L	11.4 (3.7–40.5)

Percentages are based on all patients from the included cohort excluding those with missing values (denominator shown). ALL=acute lymphoblastic leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; Ph=Philadelphia chromosome; WBC=white blood cell

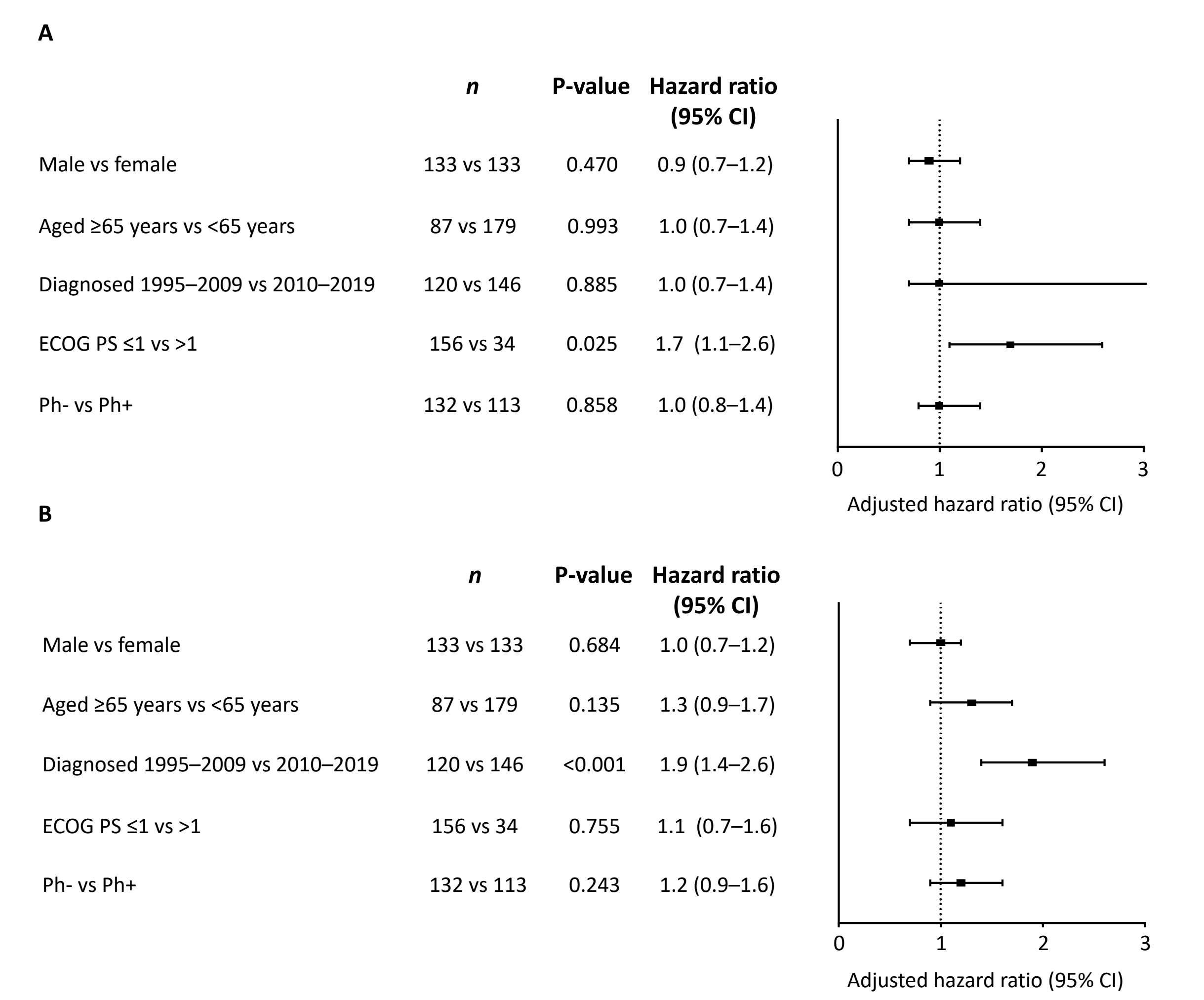
Overall Survival

- After a median follow-up of 64.2 months, median OS was 14.9 months (95% confidence interval [CI], 12.3–20.8)
  - 1-year OS rate: 56.3% (95% CI, 50.5–62.7)
  - 5-year OS rate: 24.5% (95% CI, 19.4–31.0)
- Subgroup analyses are shown in **Figure 2**
- In a multivariate Cox model, the effect of ECOG PS ≤1 (vs >1) was significant (**Figure 3A**)
- Our analysis found no evidence of violations to the semi-Markov assumption, suggesting the clock-back estimator offers a valid evaluation of OS by receipt of HSCT; results show patients without HSCT have a median survival of 15 months from diagnosis; patients undergoing HSCT exhibit a longer median survival of 22 months

Relapse-free Survival

- After a median follow-up of 64.2 months, median RFS was 7.0 months (95% CI, 5.8–8.0)
  - 1-year RFS rate: 35.4% (95% CI, 30.0–41.7)
  - 5-year RFS rate: 14.2% (95% CI, 10.3–19.6)
- In a multivariate Cox model, the effect of earlier time period of ALL diagnosis (1995–2009 vs 2010–2019) was significant (**Figure 3B**)

Figure 3: Multivariate Cox model for (A) OS and (B) RFS



A

	n	P-value	Hazard ratio (95% CI)
Male vs female	133 vs 133	0.470	0.9 (0.7–1.2)
Aged ≥65 years vs <65 years	87 vs 179	0.993	1.0 (0.7–1.4)
Diagnosed 1995–2009 vs 2010–2019	120 vs 146	0.885	1.0 (0.7–1.4)
ECOG PS ≤1 vs >1	156 vs 34	0.025	1.7 (1.1–2.6)
Ph- vs Ph+	132 vs 113	0.858	1.0 (0.8–1.4)

B

	n	P-value	Hazard ratio (95% CI)
Male vs female	133 vs 133	0.684	1.0 (0.7–1.2)
Aged ≥65 years vs <65 years	87 vs 179	0.135	1.3 (0.9–1.7)
Diagnosed 1995–2009 vs 2010–2019	120 vs 146	<0.001	1.9 (1.4–2.6)
ECOG PS ≤1 vs >1	156 vs 34	0.755	1.1 (0.7–1.6)
Ph- vs Ph+	132 vs 113	0.243	1.2 (0.9–1.6)

Multivariate Cox model for OS and RFS adjusted for sex, age, treatment period, and Ph status. The number of observations used in the analysis for OS and RFS was N=266. HRs >1 favor the reference group. ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; OS=overall survival; Ph=Philadelphia chromosome; RFS=relapse-free survival

Other Clinical Outcomes

- Best overall response recorded after ALL diagnosis is shown in **Table 2**
- Within 3 months from diagnosis:
  - 193 (72.6%) patients achieved hematologic CR
  - 47 (17.7%) patients were MRD-negative
  - 42 (15.8%) patients achieved CR and were MRD-negative (ie, molecular CR)
- Among patients with CR recorded after diagnosis, median time to CR was 1.0 month (range, 0–47.0)

Table 2: Treatment response after ALL diagnosis

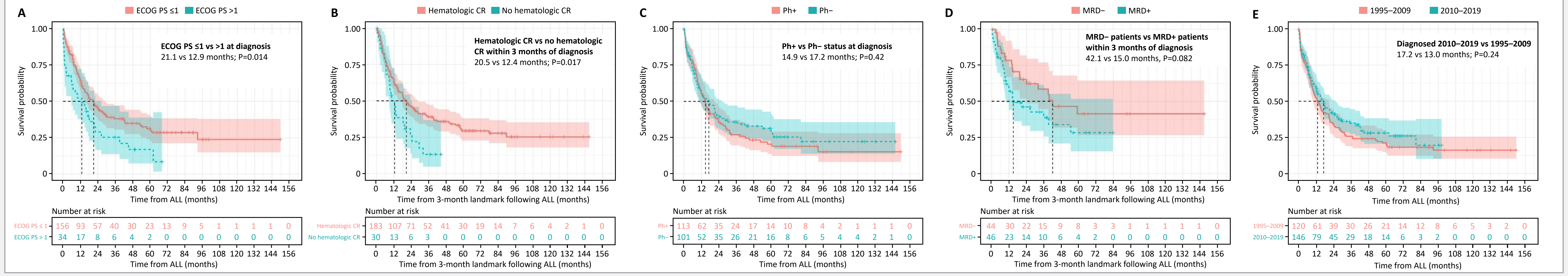
	Within 3 months	Within 1 year
Best overall response[a]	N=266	N=266
MRD-negative[b,c,d]	47 (17.7)	67 (25.2)
Hematologic CR[c,d]	108 (40.6)	111 (41.7)
Hematologic CR and MRD-positive[b,c,d]	40 (15.0)	27 (10.2)
Hematologic response[b] unknown and MRD-positive[b,d]	8 (3.0)	4 (1.5)
R/R[e]	28 (10.5)	36 (13.5)
Deceased	13 (4.9)	15 (5.6)
No assessment in the period	22 (8.3)	6 (2.3)

Best overall response mutually exclusive and ordered from best to worst response.
[a] Patients could have ≥1 response record in a given day. All response records in a given day were reviewed individually, and conflicting and incomplete response records in the same day were reconciled and classified on the basis of clinical expert review. [b-d] HARMONY database codes used to identify MRD status are shown in the **Supplementary Methods**. [e] HARMONY database codes used to identify R/R status: Hematological response to treatment; acute lymphoid leukemia relapse; bone marrow relapse; central nervous system relapse; testicle/ovary relapse; hematological relapse. CR=complete response; MRD=measurable residual disease; R/R=relapsed and/or refractory

CONCLUSIONS

- Outcomes for patients aged ≥55 years have improved over the last decades with a 1-year OS of 56%
- Outcome predictors included ECOG PS, hematologic CR, MRD-negativity, and HSCT within 1 year of diagnosis
- Presence of Ph did not stratify for OS, indicating improved outcomes with targeted therapy

Figure 2: OS stratified by (A) ECOG PS[a], (B) CR status[b], (C) Ph status[a], (D) MRD-negativity[b], and (E) Year of diagnosis



[a] At first observed ALL diagnosis date; [b] Within 3 months of ALL diagnosis. P values are from log-rank tests comparing the entire survival period. ALL=acute lymphoblastic leukemia; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; Ph=Philadelphia chromosome

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SUPPLEMENTARY MATERIAL

Supplementary Methods

HARMONY database codes used to identify measurable residual disease (MRD) status:

- Minimal residual disease by IG/TCR PCR
- Minimal residual disease by flow cytometry
- Minimal residual disease by BCR/ABL PCR
- Minimal residual disease by MLL PCR
- Minimal residual disease by PCR
- Minimal residual disease by IG/TCR flow cytometry
- Minimal residual disease by BCR/ABL flow cytometry
- Minimal residual disease by MLL flow cytometry
- Molecular response to treatment
- Minimal residual disease by IG/TCR PCR
- Minimal residual disease by flow cytometry
- Minimal residual disease by BCR/ABL PCR
- Minimal residual disease by MLL PCR
- Minimal residual disease by PCR
- Minimal residual disease by IG/TCR flow cytometry
- Minimal residual disease by BCR/ABL flow cytometry
- Minimal residual disease by MLL flow cytometry
- Molecular response to treatment
- Molecular response to treatment
- Molecular relapse
- Minimal residual disease by IG/TCR PCR
- Minimal residual disease by flow cytometry
- Minimal residual disease by BCR/ABL PCR
- Minimal residual disease by MLL PCR
- Minimal residual disease by PCR
- Minimal residual disease by IG/TCR flow cytometry
- Minimal residual disease by BCR/ABL flow cytometry
- Minimal residual disease by MLL flow cytometry

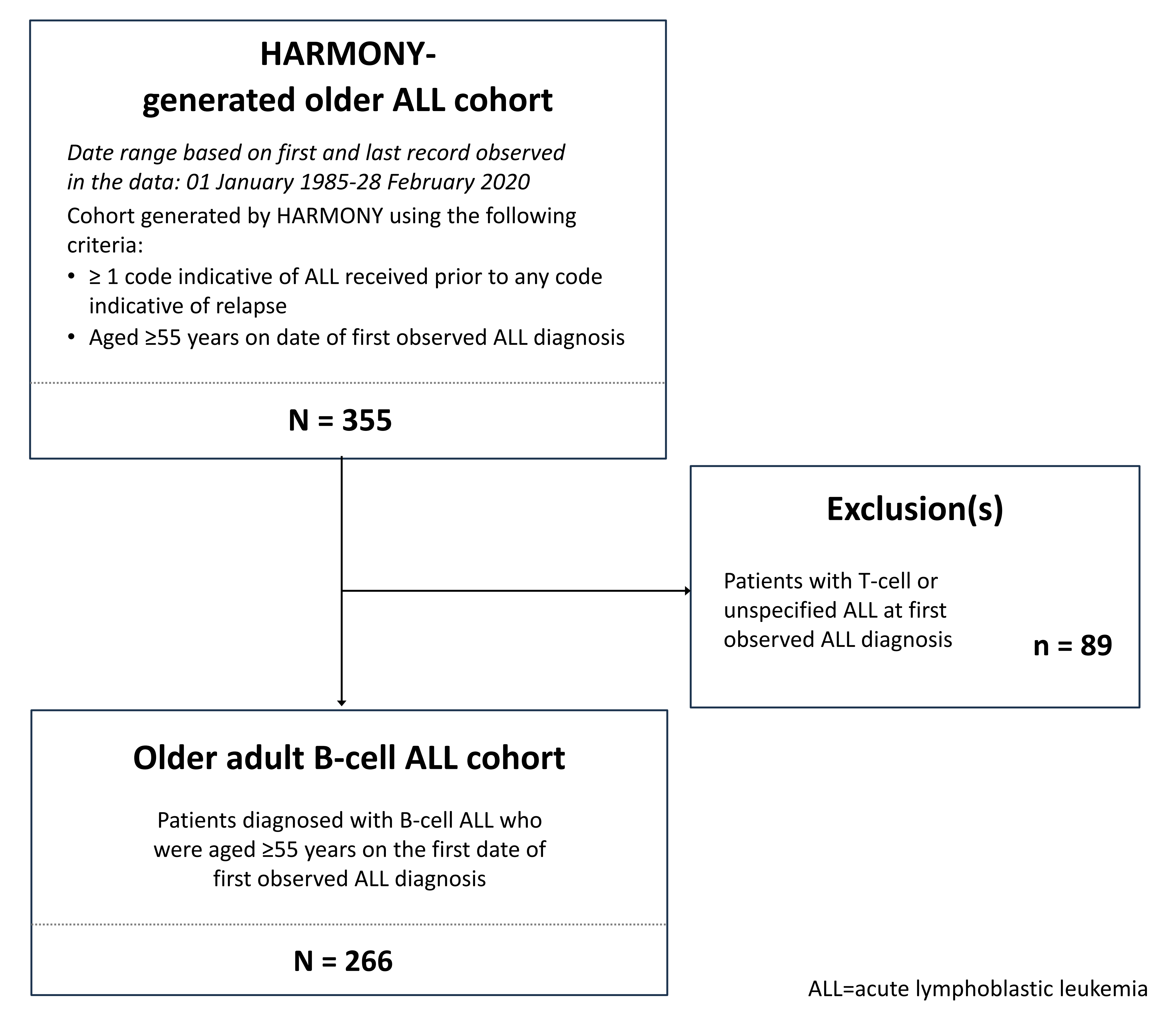
HARMONY database codes used to identify response:

- Hematological response to treatment
- Acute lymphoid leukemia in remission
- Molecular response to treatment
- Molecular response to treatment

HARMONY database codes used to identify relapsed and/or refractory status:

- Hematological response to treatment
- Acute lymphoid leukemia relapse
- Bone marrow relapse
- Central nervous system relapse
- Testicle/ovary relapse
- Hematological relapse

Supplementary Figure 1: Selection for older adult B-cell ALL cohort



HARMONY-generated older ALL cohort

Date range based on first and last record observed in the data: 01 January 1985-28 February 2020

Cohort generated by HARMONY using the following criteria:

- ≥ 1 code indicative of ALL received prior to any code indicative of relapse
- Aged ≥55 years on date of first observed ALL diagnosis

N = 355

Exclusion(s)

Patients with T-cell or unspecified ALL at first observed ALL diagnosis **n = 89**

Older adult B-cell ALL cohort

Patients diagnosed with B-cell ALL who were aged ≥55 years on the first date of first observed ALL diagnosis

N = 266

ALL=acute lymphoblastic leukemia