Title: Therapy-related acute myeloid leukemia following treatment for cancer in childhood: a population-based registry study

Running title: T-AML following childhood cancer in Australia

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Abbreviations:	ACCR	Australian Childhood Cancer Registry
	CI	confidence interval
	HSCT	hematopoietic stem cell transplantation
	SIR	standardised incidence ratio
	t-AML	therapy-related acute myeloid leukemia.

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Abstract

Background: Therapy-related acute myeloid leukemia (t-AML) is defined as AML that develops after exposure to cytotoxic chemotherapy and/or radiation therapy. There is a paucity of available literature, particularly in regard to t-AML following childhood cancer. Our aim was to describe the risk of t-AML among children treated for other cancers and their subsequent survival.

Procedure: We utilised data from the population-based Australian Childhood Cancer Registry to examine all childhood patients (<15 years at diagnosis) treated with chemotherapy and/or radiotherapy for cancers other than AML who received a subsequent diagnosis of AML between 1983-2014. Standardised incidence ratios (SIRs) were calculated to approximate the relative risk of being diagnosed with AML compared to the general population. Estimates of 5-year observed survival were obtained using the Kaplan-Meier method, with differences determined by the log-rank test.

Results: Fifty-eight of 11,753 patients in the study cohort (0.5%) were diagnosed with t-AML, an almost 50-fold higher risk than expected (SIR=45.6, 95% CI=35.3-59.0). Five-year observed survival from the date of t-AML diagnosis was 31.2% (95% CI=19.6%-43.5%). A significant survival advantage was found for patients who underwent hematopoietic stem cell transplantation (HSCT) following diagnosis of t-AML, with 5-year survival of 52.4% (29.7%-70.9%) compared to 5.7% (0.4%-22.6%) for those who did not have HSCT ($p<0.001$).

Conclusions: Although rare, t-AML is an important potential late effect of childhood cancer therapy. Prognosis is generally poor, with HSCT offering some survival benefit.

Introduction

Therapy-related acute myeloid leukemia (t-AML) is a recognised diagnosis in which AML develops in a patient previously exposed to chemotherapy and/or radiotherapy.¹ In most cases it follows the treatment of a primary malignancy or, less frequently, an autoimmune condition.

T-AML is a rare disease and has been estimated to account for approximately 10% of all AML diagnoses among adults.² It is also well established that t-AML has a poor prognosis.³ Patients with a diagnosis of t-AML are known to experience significantly inferior survival than those diagnosed with de novo AML among both adults^{4,5} and children⁶.

Not only is prognosis worse for patients diagnosed with t-AML but it appears that they are also more susceptible to toxicities associated with treatment. In patients with a history of prior chemotherapy use or radiotherapy exposure, tolerability to further treatment is reduced. Kayser et al⁵ found that in more intensely treated younger adults, treatment-related toxicity had a major negative impact on outcome and proposed that this may reflect the cumulative toxicity of cancer treatment.

Prior use of alkylating agents, radiation therapy and/or topoisomerase II inhibitors appears to carry the greatest risk for development of t-AML.⁷ T-AML occurring after use of these agents is associated with certain chromosomal and cytogenetic abnormalities not as commonly seen in de novo AML. Such abnormalities seem to confer adverse risk and increased likelihood of relapse.⁸

The latency period between the primary diagnosis requiring chemotherapy and/or radiotherapy and the development of t-AML varies considerably from a few months to many years. Risk for development of t-AML and the latency period both appear to be associated with the type of chemotherapeutic agent used, the timing of exposure and dose of agent used.⁹

Due to the rarity of t-AML diagnoses following childhood cancer, much remains to be studied in terms of patient cohort characteristics and prognosis. Our study aimed to utilise a national, population-based dataset to describe the risk of t-AML among a cohort treated for other childhood cancers and their subsequent survival.

Methods

Data

A retrospective analysis was conducted of de-identified longitudinal data from the Australian Childhood Cancer Registry (ACCR). Information on all notified cases of cancer for children aged 0-14 at diagnosis is collected from the population cancer registries in each Australian State and Territory under appropriate ethics and legislative approvals. Cancer type was defined according to the International Classification of Childhood Cancers, third edition (ICCC-3).¹⁰ Cases held by the ACCR are matched annually against the Australian Cancer Database and the National Death Index to ensure that all subsequent cancers diagnosed at any age are recorded in the ACCR database and that mortality status is updated. Treatment details are also collected by the ACCR for all cancers diagnosed before 15 years of age.

The study cohort included children (aged <15 years) who were diagnosed with a first primary cancer (other than AML) during the period 1983-2012 and treated with chemotherapy and/or radiotherapy. Exclusion criteria were a first diagnosis of AML, the first primary malignancy was diagnosed prior to 1983, if the patient was from overseas but treated in Australia, or if the start date of treatment was not recorded.

Unique registry numbers were used to match first and second cancers for the same patient, with follow-up available to 31 Dec 2014. Any AML that was subsequently diagnosed within this cohort

was taken to be t-AML i.e. morphology code of AML (ICD-O-3 codes 9840, 9861, 9866, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920 or 9931) any time after the initiation of chemotherapy or radiation for the first primary cancer.

Analysis

For each childhood cancer patient who received chemotherapy or radiotherapy, their time at risk (follow-up) was calculated from date of first treatment until either the end of the study period (31 December 2014), date of death or date of diagnosis of t-AML, whichever came first. The maximum possible age at diagnosis for t-AML was 46 (for a 14-year-old diagnosed with a first cancer during 1983 and diagnosed with t-AML in 2014). Given that an open-ended follow-up period may be expected to somewhat dilute the results, analyses were also performed with follow-up arbitrarily finishing at the patient's 25th birthday for comparison. Age-adjusted incidence rates of t-AML were calculated, using the time at risk as the denominator and standardised to the 2000 World Standard Population.

Standardised incidence ratios (SIRs) were used to approximate the risk of developing t-AML following treatment with either chemotherapy or radiotherapy, relative to the incidence of AML within the general population. The expected number of second primary cancers was calculated by multiplying the time at risk (in years) by the incidence rate of AML experienced by the general population in Australia, matched by sex, 5-year age group and calendar year. Incidence rates were averaged over blocks of 4 calendar years to produce more stable estimates. SIRs were then obtained by dividing the observed number of t-AML cases by the expected number. The cumulative incidence function for t-AML was also calculated, with any death considered as a competing risk.

Five-year observed survival was calculated from date of diagnosis of t-AML using the Kaplan-Meier method. Survival time was censored at either 31 Dec 2014 or 5 years from the date of t-AML

diagnosis (whichever occurred first) for patients who remained alive at those time points. Minimum follow-up from the date of diagnosis of t-AML for a patient who was still alive as at 31 Dec 2014 was 7 months. Relapse was not considered as a competing event. Differences in unadjusted survival by key variables of interest were assessed using the log-rank test.

Point estimates for SIRs and survival, along with 95% confidence intervals (95% CIs), were calculated for key demographic and clinical variables of interest including sex, age group, time period of diagnosis, broad type of first cancer and treatment received. Note that treatment details for t-AML were only collected in the ACCR for patients diagnosed with t-AML before 15 years of age. All data analysis was performed using Stata SE for Windows v15 software. Specific ethics approvals were not required for this study as it was conducted using de-identified data only.

Results

Study cohort

A total of 17,269 Australian children aged 0-14 were diagnosed with a cancer other than AML between 1983 to 2012, with 11,782 reported to have been treated with chemotherapy and/or radiotherapy. The start date of treatment was unknown for 29 children, leaving 11,753 patients who were eligible for follow-up (68% of all children with cancer). Total follow-up time for incident t-AML was 141,745 years, with a median of 10.3 years (interquartile range = 3.6 years to 19.5 years).

Of the 11,753 eligible patients, 58 (0.5%) were diagnosed with t-AML by 31 December 2014. The age-standardised incidence rate of t-AML among those at risk was 24.1 per 100,000 person years (95% CI = 18.1-31.5). Most t-AML cases (n=45, 78%) were diagnosed within 5 years of the first primary cancer, with a median time between the commencement of treatment for the first cancer to diagnosis of t-AML of only 2.4 years (interquartile range = 1.9 years to 4.6 years). Although follow-up was available to a maximum age of 46 for some patients, no cases of t-AML were

diagnosed after the age of 24, emphasising that t-AML was most likely to occur relatively soon after treatment for the original cancer. Truncating follow-up at each patient's 25th birthday gave an age-standardised incidence rate of 44.0 per 100,000 person years (95% CI = 32.9-57.4).

Only 8 out of the 58 t-AML cases (14%) had a morphology code of M99203 (therapy-related AML). The most common morphology given in the pathology reports was M98613 (acute myeloid leukemia not otherwise specified) with 25 cases (43%) followed by 10 cases (22%) which were coded as M98913 (acute monocytic leukemia).

Incidence distribution and relative risk of t-AML

Childhood cancer patients treated with chemotherapy and/or radiotherapy had a greatly increased risk of subsequently being diagnosed with AML (SIR = 45.6, 95% CI = 35.3-59.0) compared to the general population (Table 1). If follow-up time was capped at each person's 25th birthday the SIR rose to 56.0 (95% CI = 43.3-72.5). Twenty-year cumulative incidence was 0.7% (95% CI = 0.5%-1.0%).

The number of males diagnosed with t-AML (n=39, 67% of t-AML diagnoses) was around double the number of females (n=19) (Table 1). However, despite the suggestion that males were at an increased relative risk of developing t-AML following childhood cancer compared to females, with SIRs of 52.7 and 35.7 respectively, the small number of cases available meant that the resulting SIR ratio of 1.48 for males:females was not statistically significant (95% CI = 0.83-2.70; $p = 0.20$). Approximately half (47%) of those in the cohort who developed t-AML were aged 0-4 years at the time of their first cancer diagnosis, consistent with the median age of 5 years for all childhood cancers.

The type of first cancer was evenly divided between blood cancers (excluding AML) and solid tumours. More specifically, the most common original cancers were acute lymphoid leukemia (n=21, 36%), Ewing bone tumours and rhabdomyosarcoma (both n=6, 10%). There was no clear evidence of any difference in the relative risk of t-AML depending on the broad type of first cancer, with the SIR ratio for blood cancers (excluding AML):solid tumours = 0.79 (95% CI = 0.46-1.37, p = 0.44).

Treatment

As shown in Table 1, nearly all (n=57, 98%) patients who were diagnosed with t-AML received chemotherapy for their first cancer, 20 (34%) were treated with radiotherapy and 7 (12%) underwent hematopoietic stem cell transplantation (HSCT) using bone marrow or peripheral stem cells. Of note, the SIR for t-AML among children following HSCT for their first cancer was more than double that of the study cohort in general at 120.7 (95% CI = 57.5-253.2).

Treatment details for the t-AML were also available for the 44 children who were diagnosed with t-AML prior to reaching 15 years of age. Of these patients, 33 (75%) received chemotherapy coupled with either HSCT (n=21, 48%) and/or radiotherapy (n=5, 11%) as part of their t-AML therapy. The remaining 11 children (25%) had none of these treatments recorded following diagnosis with t-AML. Complete remission was achieved by 23 of 40 (58%) t-AML patients aged under 15 where the remission status was recorded, including 19 of 21 (90%) treated with HSCT compared to only 4 of 19 children (21%) who were not given HSCT (p<0.001).

Survival

Almost three-quarters of the cohort (41 out of 58, 71%) had died by the end of the study period (31 December 2014). The majority of these deaths (n=38, 93%) occurred within 2 years of t-AML diagnosis. Five-year observed survival was 31% from the time of t-AML diagnosis (Fig 1).

No significant disparities in survival following t-AML were recorded by sex, age at t-AML diagnosis, time from first diagnosis to t-AML diagnosis, year of t-AML diagnosis or type of first cancer (Table 2 and Fig 2), although this appeared to be partly due to the small number of cases available. For example, 5-year observed survival was more than double for females compared to males (50% versus 23%), but the difference failed to reach statistical significance ($p=0.08$).

Both chemotherapy and HSCT following t-AML were, however, associated with a survival advantage among those patients for whom this information was available (i.e. diagnosed with t-AML before 15 years of age). Of particular interest, 5-year observed survival was 52% for the group who had HSCT in contrast to 6% for children who did not receive HSCT to treat t-AML ($p<0.001$). All of the 14 children aged under 15 who did not achieve remission following t-AML died within two years of diagnosis (Table 2).

Discussion

Using a population-based cohort, we provide here the first description of the relative risk of t-AML being diagnosed following treatment for childhood cancer; to the best of our knowledge, this information has never been previously reported in either a paediatric or adult setting. Although the absolute risk was small, our finding that survivors who were treated with chemotherapy and/or radiotherapy had an almost 50-fold increased risk compared to those without cancer helps to quantify the impact that childhood cancer can have beyond the initial diagnosis. This is especially pertinent given that AML is one of the most commonly diagnosed malignancies among childhood cancer survivors, accounting for 15% of all second primary cancers in Australia.¹¹

While caution is needed when interpreting results based on a small number of cases, our finding that males comprise two-thirds of t-AML cases following childhood cancer is worth some

consideration, particularly when paired with the suggestions (although not statistically significant) that males may also be at higher relative risk and have a worse prognosis than females. Comparable distributions by sex have been reported among pediatric t-AML patients in the United States⁶ and Japan¹². Interestingly, this is in direct contrast to results seen in adult studies on t-AML which show a clear female predominance.^{13,14} A Swedish study¹⁴ assumed that the female excess seen in the number of adult t-AML cases was a by-product of the fact that breast cancer was the most prevalent cancer in that population, thereby allowing a greater opportunity for t-AML to develop among females. Similarly, the excess of young males with t-AML may be at least partly accounted for by childhood cancer being somewhat more common among males than females (55% vs 45% in Australia)¹¹; even so, this does explain why t-AML appears to pose more of a risk among male survivors of paediatric cancer. Further investigation in other populations is warranted.

The current study is in line with information provided on adult cohorts which show that t-AML arises in equal proportions from primary hematological malignancies as it does from primary solid tumours.⁸ Half of the childhood cancer patients developed t-AML between 2-5 years after first diagnosis, which is also in keeping with prior adult studies that found a median latency period of 4-5 years.¹⁵

A few studies conducted using surveys of hospital-based series of pediatric patients have focused on outcomes for this group^{6,12,16-19}, but some of the findings are difficult to interpret as t-AML tends to be mixed in with other therapy-related cancers. Further, each of these studies involved a very small number of t-AML patients (range of 16¹⁸ to 36¹⁹). Our findings, examining how survival varies by key patient and clinical characteristics using the largest cohort of childhood cancer survivors diagnosed with t-AML that have been studied to date, therefore add valuable information to the limited existing literature.

In particular, the current study substantiates the poor prognosis associated with a diagnosis of t-AML following childhood cancer; five-year observed survival for t-AML was 31% compared to a recent estimate of 77% for 5-year relative survival following childhood AML in Australia.²⁰ We were also able to verify a striking 5-year survival benefit when HSCT was used to treat t-AML. Our results are consistent with studies elsewhere^{6,12,16-18} that have demonstrated the therapeutic benefits of HSCT for paediatric t-AML patients. These collective findings indicate that therapy for t-AML in children should be with the aim of achieving remission and bridging patients to HSCT. Given the high mortality associated with t-AML and with our study identifying HSCT as an effective therapy, it seems prudent that children should be prepared for HSCT as soon as possible after a diagnosis of t-AML to increase their chance of survival. Some authors^{17,19} do, however, warn of high rates of non-relapse mortality following transplant.

It is important to acknowledge that we are unable to rule out potential confounding factors associated with the use of HSCT. Perhaps the most notable is our inability to report on why certain paediatric patients were offered HSCT and others where not. For example, if the reason patients were not offered HSCT was because they were too unwell or that they died before it was possible to perform the procedure then our finding may simply represent their pre-existing poor condition rather than the effectiveness of HSCT as a therapy for t-AML. Furthermore, it has been shown that outcomes following HSCT in AML are inferior when performed in the setting of refractory disease, particularly for children aged over 10 years with > 30% blasts in the bone marrow,²¹ so it is likely that patients failing to achieve remission after initial chemotherapy were either not offered or declined HSCT. Our results should also be interpreted with the understanding that HSCT is continually being refined,²² with studies demonstrating a clear trend towards a reduction in transplant-related mortality over time.²³⁻²⁵ As such, it is likely that success rates will continue to increase into the future and so the survival benefit of HSCT may actually be greater than what we report here over the previous three decades. Unfortunately, we were unable to investigate whether

survival rates for HSCT have improved over time as there was an insufficient number of cases to stratify survival following HSCT by the period of t-AML diagnosis.

A strength of our study is that the ACCR is population-based, allowing us to draw conclusions at a national level. Using data from the ACCR also allowed us the benefit of having a longitudinal approach over a 30 year period. This meant we were able to report on the temporal relationship between primary cancer diagnosis, t-AML diagnosis and 5-year survival outcomes.

Use of morphology code M99203 (therapy-related AML) is recommended for accurate identification of t-AML patients. One potential limitation of our study is that very few patients had the appropriate morphology code and instead we had to make the reasonable assumption that any diagnosis of AML following treatment with chemotherapy and/or radiotherapy constituted t-AML. We therefore cannot rule out that some cases of paediatric t-AML may have been either missed or mis-identified. Imprecision in coding is likely to hinder research into t-AML when relying on cancer registry data, as comprehensive treatment data is often lacking.

Similarly, it is recognised that t-AML can occur after non-malignant primary diagnoses that also require chemotherapy or radiotherapy as treatment, particularly autoimmune conditions.²⁶ The ACCR is a cancer database only and as such other primary diseases are not recorded. We may be missing a small number of patients who developed t-AML after treatment for a non-malignant condition and these children may have different characteristics and associated prognosis.

Finally, the statistical power of our analysis has been restricted by the small number of t-AML cases available for study, making it difficult to detect differences in the SIRs and survival estimates when stratified by key variables of interest. It was also not feasible to apply multivariate models to the data to calculate adjusted survival for this reason.

In conclusion, t-AML is a rare disease with relatively short latency from a prior cancer diagnosis. Although the prognosis is poor for most patients, our results indicate that a significant number can be salvaged with HSCT. Advances in HSCT techniques which increase donor options, such as haploidentical transplantation, may improve outcomes for those who respond to induction therapy and can undergo the procedure.

Conflict of interest statement: The authors have no competing interests to disclose.

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Figure 1 Kaplan-Meier observed survival curves for t-AML following childhood cancer in Australia, 1982-2014. 95% confidence intervals for the survival point estimates are shown in shading.

Figure 2 Kaplan-Meier observed survival curves for t-AML following childhood cancer in Australia, 1982-2014 by: A) sex; B) age at t-AML diagnosis; C) time period of t-AML diagnosis; D) type of first cancer; E) chemo-therapy following t-AML diagnosis and F) HSCT treatment following t-AML diagnosis. P-values for equality of survivor functions calculated using the log-rank test. Solid tumours include cases of medulloblastoma, primitive neuroectodermal tumor, neuroblastoma, nephroblastoma, hepatic carcinoma, osteosarcoma, Ewing tumour, unspecified malignant bone tumour, rhabdomyo-sarcoma, non-rhabdomyosarcoma soft tissue sarcoma and intracranial and intraspinal germ cell tumours. Treatment received for t-AML was only available for the 44 children who were diagnosed with t-AML before 15 years of age.

TABLE 1 Counts and standardised incidence ratios for the diagnosis of t-AML following a first primary childhood cancer (other than AML), by demographic and clinical characteristics, Australia, 1983-2014^a

Characteristic	n	%	SIR (95% CI)
Total	58	100	45.6 (35.3-59.0)
<i>Sex</i>			
Males	39	67	52.7 (38.5-72.1)
Females	19	33	35.7 (22.8-56.0)
<i>Age at first diagnosis</i>			
0-4 years	27	47	43.8 (30.1-63.6)
5-9 years	14	24	43.3 (25.6-73.0)
10-14 years	17	29	51.2 (31.8-82.4)
<i>Age at diagnosis of t-AML</i>			
0-4 years	5	9	n.a.
5-9 years	23	40	n.a.
10-14 years	16	28	n.a.
15-24 years	14	24	n.a.
25-46 years	0	0	n.a.
<i>Time from first diagnosis to t-AML diagnosis</i>			
Less than 2 years	16	28	n.a.
2 years to less than 5 years	29	50	n.a.
5 or more years	13	22	n.a.
<i>Type of first cancer</i>			
Blood cancer (excluding AML)	29	50	40.8 (28.3-58.7)
- Acute lymphoblastic leukemia	21	36	42.0 (27.4-64.5)
- Lymphoma	8	14	40.0 (20.0-80.0)
Solid tumours ^b	29	50	51.7 (36.0-74.5)
<i>Treatments received for first cancer</i>			
Chemotherapy	57	98	49.0 (37.8-63.6)
Radiation therapy	20	34	41.2 (26.6-63.9)
HSCT	7	12	120.7 (57.5-253.2)
<i>Treatments received for t-AML^c</i>			
Chemotherapy	33	75	n.a.
Radiation therapy	5	11	n.a.
HSCT	21	48	n.a.

Abbreviations: SIR, standardised incidence ratio; CI, confidence interval; n.a., not applicable; HSCT, Hematopoietic stem cell transplant.

Notes: a. Diagnosis of first primary childhood cancer (other than AML) occurred between 1983-2012 with follow-up for t-AML diagnosis to 31 Dec 2014. b. Solid tumours include cases of astrocytoma, medulloblastoma, primitive neuroectodermal tumor, neuroblastoma, nephroblastoma, hepatic carcinoma, osteosarcoma, Ewing tumour, unspecified malignant bone tumour, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma and intracranial and intraspinal germ cell tumours. c. Information on treatments received for t-AML was only available for the 44 children who were diagnosed with t-AML before 15 years of age.

TABLE 2 Five-year observed survival from date of diagnosis of t-AML by selected characteristics, Australia, 1983-2014^a

Characteristic	Patients	Deaths (within 5 years)	Five-year observed survival (95% CI)	p-value
Total	58	39	31.2% (19.6%-43.5%)	n.a.
<i>Sex</i>				
Males	39	30	23.1% (11.5%-37.1%)	0.08
Females	19	9	49.8% (25.3%-70.2%)	
<i>Age at diagnosis of t-AML</i>				
0-14 years	44	30	29.5% (16.6%-43.6%)	0.95
15-24 years	14	9	35.7% (13.0%-59.4%)	
<i>Time from first diagnosis to t-AML diagnosis</i>				
Less than 2 years	16	10	35.2% (13.3%-58.2%)	0.19
2 years to less than 5 years	29	23	20.7% (8.4%-36.7%)	
5 or more years	13	6	51.9% (22.5%-75.0%)	
<i>Time period of t-AML diagnosis</i>				
1983-1997	25	20	20.0% (7.3%-37.2%)	0.22
1998-2014	33	19	40.9% (23.9%-57.2%)	
<i>Type of first cancer</i>				
Blood cancer (excluding AML)	29	22	24.1% (10.7%-40.6%)	0.48
Solid tumours ^b	29	17	39.3% (21.4%-56.7%)	
<i>Chemotherapy following t-AML diagnosis^c</i>				
Yes	33	21	34.9% (19.2%-51.1%)	0.004
No	11	9	12.1% (0.7%-40.4%)	
<i>HSCT following t-AML diagnosis^c</i>				
Yes	21	10	52.4% (29.7%-70.9%)	<0.001
No	23	20	5.7% (0.4%-22.6%)	
<i>Remission status^d</i>				
Yes	26	15	42.3% (23.5%-60.0%)	<0.001
No	14	14	0% (n.a.)	

Abbreviations: CI, confidence interval; n.a., not applicable, HSCT, hematopoietic stem cell transplant; n.a. = not applicable

Notes: a. Diagnosis of first primary childhood cancer (other than AML) occurred between 1983-2012 with follow-up on t-AML diagnosis and mortality status to 31 Dec 2014. b. Solid tumours include cases of astrocytoma, medulloblastoma, primitive neuroectodermal tumor, neuroblastoma, nephroblastoma, hepatic carcinoma, osteosarcoma, Ewing tumour, unspecified malignant bone tumour, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma and intracranial and intraspinal germ cell tumours. c. Treatment received for t-AML was only available for the 44 children who were diagnosed with t-AML before 15 years of age. d. Remission status following t-AML was only available for 40 of the 44 children who were diagnosed with t-AML before 15 years of age.