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Early mortality and complications in hospitalized adult Californians with acute myeloid leukaemia

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Summary

Few studies have evaluated the impact of complications, sociodemographic and clinical factors on early mortality (death ≤60 days from diagnosis) in acute myeloid leukaemia (AML) patients. Using data from the California Cancer Registry linked to hospital discharge records from 1999 to 2012, we identified patients aged ≥15 years with AML who received inpatient treatment ($N = 6359$). Multivariate logistic regression analyses were used to assess the association of complications with early mortality, adjusting for sociodemographic factors, comorbidities and hospital type. Early mortality decreased over time (25·3%, 1999–2000; 16·8%, 2011–2012) across all age groups, but was higher in older patients (6·9%, 15–39, 11·4%, 40–54, 18·6% 55–65, and 35·8%, >65 years). Major bleeding [Odds ratio (OR) 1·5, 95% confidence interval (CI) 1·3–1·9], liver failure (OR 1·9, 95% CI 1·1–3·1), renal failure (OR 2·4, 95% CI 2·0–2·9), respiratory failure (OR 7·6, 95% CI 6·2–9·3) and cardiac arrest (OR 15·8, 95% CI 8·7–28·6) were associated with early mortality. Higher early mortality was also associated with single marital status, low neighbourhood socioeconomic status, lack of health insurance and comorbidities. Treatment at National Cancer Institute-designated cancer centres was associated with lower early mortality (OR 0·5, 95% CI 0·4–0·6). In conclusion, organ dysfunction, hospital type and sociodemographic factors impact early mortality. Further studies should investigate how differences in healthcare delivery affect early mortality.

Keywords: AML, epidemiology, outcomes research, acute leukaemia, early mortality.

Acute myeloid leukaemia is associated with a poor overall prognosis, especially in older adults. Survival decreases with age, with 5-year relative survival of 65·9% in patients aged less than 15 years old, 49·9% in patients aged 15–39 years old and 16·7% in older adults (Siegel *et al*, 2015; Keegan *et al*, 2016). Initial standard treatment of AML consists of induction chemotherapy, which usually requires an inpatient hospitalization of at least 1 month, a period that is associated with a high early mortality both due to the underlying disease and complications of treatment (Walter *et al*, 2011). Early mortality has been reported to occur primarily from infection, bleeding or hyperleucostasis (Ferrara & Schiffer, 2013).

Recent studies have shown an improvement in early mortality, defined as death within the first 30- or 60-days of diagnosis, over the past few decades (Appelbaum *et al*, 2006; Othus *et al*, 2014; Percival *et al*, 2015). This improvement may be related to advances in supportive care in patients undergoing intensive chemotherapy, including rigorous transfusions and advancements in the prevention and treatment of infections, specifically with newer antifungal therapy (Higby *et al*, 1974; Walsh *et al*, 1999; Cornely *et al*, 2007). However, improvements in early mortality may not be occurring among all patients, as recent studies have highlighted the disparities in long-term survival between different patient populations, with public or lack of insurance coverage, African-African race/ethnicity and lower income all associated with inferior long-term survival (Kristinsson *et al*, 2009; Bierenbaum *et al*, 2012; Patel *et al*, 2015).

Few studies have examined the types of complications that have impacted AML patients in the last 15 years and how these complications and sociodemographic and clinical factors contribute to early mortality. Prior studies have evaluated the rates of febrile neutropenia, bleeding and invasive fungal infections in AML patients, but these were primarily
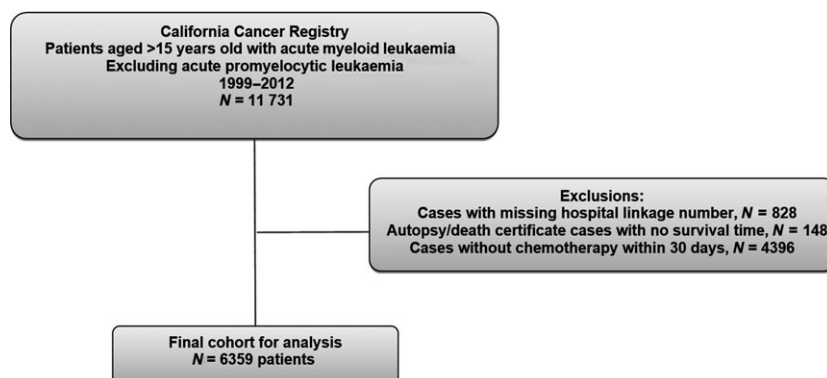
Fig 1. Analysis cohort of patients with acute myeloid leukaemia in California.

in the clinical trial setting or were single centre studies and did not present differences by age (Camera *et al*, 2003; Lowenberg *et al*, 2011; De Rosa *et al*, 2013; Ferrara & Schiffer, 2013; Garcia *et al*, 2013; Buckley *et al*, 2014). To our knowledge, no population-based studies have considered the effect of complications on early mortality in AML patients (Juliusson *et al*, 2012). Because early mortality continues to be a barrier to improving long-term survival and age is a major prognostic factor (Juliusson *et al*, 2009), evaluating the factors that impact early mortality on a population-based level will identify targeted areas for improvement.

Therefore, we examined trends in 60-day mortality, complications requiring any hospitalization within 60 days of diagnosis, and sociodemographic and clinical factors associated with 60-day mortality among adult AML patients by age. We hypothesized that early mortality and medical complications would be higher in older patients and sociodemographic factors would be more strongly associated with early mortality among younger patients.

Methods

Study population

Adolescent and adult patients (>15 years of age) diagnosed with a first primary AML and treated at a hospital in California from 1999 to 2012 were eligible for the study. To identify cases of AML, we used the following morphology codes from the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (WHO, 2000): 9840, 9861, 9867, 9869–9874, 9891, 9895–9898, 9910, 9911, 9920 and 9931. We excluded patients with a diagnosis of acute promyelocytic leukaemia because the treatment and management differs from AML. We also excluded children because the treatment and biology may be different in this group. In addition, we excluded patients without a record linkage number to hospital data; with an AML diagnosis at autopsy or death certificate only; who did not receive chemotherapy within 30 days of diagnosis as indicated in either databases; and without an inpatient hospitalization (Fig 1). Our final cohort included 6359 AML patients.

Databases

This study used a linked database between the California Cancer Registry (CCR) and the California Office of Statewide Health Planning and Development Patient Discharge Database (PDD) (http://www.ccrcal.org/Data_and_Statistics/Cancer_Data_for_Research.shtml). The CCR contains sociodemographic and clinical information on all patients diagnosed with cancer in California. Reporting is mandatory and completeness of cases is at least 98%. From the CCR, we obtained information on age at diagnosis, race/ethnicity, year of diagnosis, gender, marital status, neighbourhood socioeconomic status (SES), health insurance at diagnosis or initial treatment and date of initial chemotherapy.

The PDD contains information about all patients hospitalized in the state, except patients admitted to one of 14 Federal hospitals (12 Veterans Affairs hospitals and two military hospitals). Serial records from a single person are linked using an encrypted form of the social-security number, called the record linkage number (Grannis *et al*, 2002; Hser & Evans, 2008). PDD records include a principal medical diagnosis, up to 24 additional 'secondary' diagnoses, and a principal and up to 20 secondary procedures coded using International Classification of Diseases, 9th Revision, Clinical Modification codes (ICD-9-CM). From the PPD, we obtained information on complications, chemotherapy administration, leukapheresis (a procedure used as a surrogate for hyperleucocytosis; ICD-9, 99·72), and comorbidities 2 years prior to or at AML diagnosis using the Elixhauser index (Schoenman *et al*, 2007). The database also includes a hospital identifier. From this list of hospitals, we were able to classify hospitals into those associated with a National Cancer Institute (NCI)-designated cancer centre, Kaiser (a large vertically integrated health organization in California), teaching (academic centres without NCI designation) and private non-academic hospitals.

Outcomes

The primary outcome was death ≤60 days from AML diagnosis. Secondary outcomes were the following complications: major bleeding, sepsis, venous thrombosis, renal failure, liver

dysfunction, respiratory failure, or cardiac arrest (ICD-9 codes in Table SI). These complications were chosen as they have been previously identified in prior studies as being primary complications during AML induction treatment (Ferrara & Schiffer, 2013). Complications were included if they occurred within any hospitalization from the time of diagnosis to 60 days or death.

Statistical analysis

Chi-square tests were used to assess differences in complications and mortality by age group. Multivariate logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) to assess the associations between sociodemographic and clinical factors, including complications, with early mortality. Interactions by age were examined for each variable in the model. Analyses were performed using SAS® (9.4) software (SAS Institute, Cary, NC, USA) and a two-sided $P < 0.05$ was considered statistically significant, including interactions.

Results

From 11 731 patients with AML, we identified 6359 patients that fulfilled our inclusion criteria (Fig 1). While most younger patients (84·5% aged 15–39 years, 80·8% aged 40–54 years, 75·5% aged 55–65 years) were hospitalized for chemotherapy, only 40·4% of AML patients aged >65 years were hospitalized and received chemotherapy and included in this study. The proportion of AML patients aged >65 years that were hospitalized and received chemotherapy did not substantially change from 1999 to 2012 (Table SII). The majority of the 6359 patients in our analytic cohort were white (61·4%), married (59·4%), had private insurance (50·8%) and were treated at a private hospital (45·9%) (Table I). Seventy-nine per cent of patients had at least one comorbidity prior to or at diagnosis. Only 3·5% of the patients underwent leukapheresis. When evaluating by age, a greater percentage of younger patients, aged 15–39 years, lived in lower SES neighborhoods, had public insurance and were treated at an NCI-designated cancer centre when compared to those >65 years old.

For patients of all ages, there was an overall decrease in 60-day mortality from 1999 to 2012 (Fig 2). While those aged >65 years had the highest early mortality rate, this cohort also had the greatest absolute decrease in early mortality over time from 43% in 1999–2002 to 28% in 2010–2012. In the younger cohort, aged 15–39 years, the relative 60-day mortality decreased by more than 50% from 1999 to 2012. There were differences in the rate of early mortality by WHO/French-American-British (FAB) classifications, with a range of 11% in AML with t(8;21)(q22;q22) up to 26% in those with AML-M7 subtype (Table SIII).

The majority of complications across all ages were sepsis (35%), major bleeding (12%), renal failure (18%) and respiratory failure (12%) (Table II). Complications were similar across all age groups, except that those aged 55–65 years had higher rates of most complications than patients of other ages (sepsis 40·6%, $P < 0.001$; venous thrombosis 2·4%, $P = 0.003$; renal failure 21·7%, $P < 0.001$; and respiratory failure 17%, $P < 0.001$). Complications were also similar across racial/ethnic groups, except that African Americans had higher rates of renal failure, Hispanics had higher rates of sepsis and Asians had higher rates of respiratory failure (Table SIV).

In multivariate analyses, age was associated with 60-day mortality, with those of younger age having lower odds of dying within 60-days compared to those >65 years of age (Table III). African American (OR = 0·66; 95% CI: 0·46, 0·94) patients also had a lower odds of dying within 60-days compared to non-Hispanic white patients. Improvements in early mortality occurred after 2002. Higher 60-day mortality was also associated with single marital status, low neighbourhood SES, and lack of health insurance. Increasing number of comorbidities (versus none) was also associated with increased early mortality, with higher mortality in those with ≥3 comorbidities (OR = 1·97, 95% CI: 1·56, 2·49) than 1–2 comorbidities (OR = 1·46, 95% CI: 1·16–1·84).

Significant interactions by age were only found for marital status ($P < 0.001$). Single marital status was only significantly associated with increased odds of early mortality in those aged >65 years (OR 1·37, 95% CI: 1·09–1·71) (data not shown in Tables). In those aged 40–54 years, lack of health insurance (OR 5·81, 95% CI: 2·26–14·30) was associated with increased odds of early mortality compared to private health insurance.

Across all age groups, the complications of bleeding, liver, renal, respiratory failure and cardiac arrest were associated with a higher OR of dying within 60 days (Table III). There were no significant differences by age group, except that respiratory failure (OR = 13·00, 95% CI: 6·14–27·53) and bleeding (OR = 2·69, 95% CI: 1·38–5·25) had higher odds of 60-day mortality in patients 15–39 years of age (data not shown in tables). Treatment at an NCI-designated cancer centre (versus private hospital) was associated with lower odds of dying within 60-days (OR=0·45, 95% CI: 0·36, 0·56). There were no differences in mortality between the other hospital types.

Table IV shows the number of complications by hospital type. Private hospitals had higher rates of sepsis ($P < 0.001$), bleeding ($P = 0.001$) and cardiac arrest ($P < 0.001$). Renal failure accounted for more than a fifth of all complications in those treated at teaching and NCI-designated cancer centres.

Discussion

In our analysis using a large, sociodemographically and geographically diverse cohort of hospitalized AML patients

Table I. Sociodemographic and clinical characteristics of hospitalized acute myeloid leukaemia patients receiving chemotherapy by age at diagnosis, California, 1999–2012.

Variables	Total N = 6359 (%)	15–39 N = 1059 (%)	40–54 N = 1479 (%)	55–65 N = 1556 (%)	>65 N = 2265 (%)	*P*-value
Gender						
Male	55·4	51·3	52·1	56·8	58·6	<0·0001
Female	44·6	48·7	47·9	43·2	41·4	
Race/ethnicity						
Non-Hispanic white	61·4	42·2	55·1	65·8	71·5	<0·0001
African American	5·3	6·2	7·4	5·3	3·7	
Hispanic	19·7	34·7	22·3	16·7	13·0	
Asian	13·0	15·8	14·9	11·9	11·3	
Year of diagnosis						
1999–2002	29·3	28·8	29·9	26·5	31·2	0·020
2003–2006	26·9	27·7	28·1	28·0	25·0	
2007–2009	22·5	22·9	22·9	22·0	22·3	
2010–2012	21·3	20·7	19·1	23·6	21·5	
Comorbidities						
0 comorbidities	21·1	33·0	27·2	17·0	14·5	<0·0001
1–2 comorbidities	43·2	45·9	46·0	44·7	39·1	
3+ comorbidities	35·7	21·2	26·8	38·4	46·4	
Marital status at diagnosis						
Married	59·4	37·9	63·7	67·1	61·4	<0·0001
Single marital status	39·0	60·5	35·1	30·9	37·0	
Neighbourhood socioeconomic status						
Low	52·7	61·8	53·6	52·2	48·2	<0·0001
High	45·3	37·1	44·5	46·1	49·2	
Health insurance status						
Public insurance	12·8	26·4	18·8	12·4	2·7	<0·0001
Private insurance	50·8	58·6	66·5	62·9	28·7	
Medicare	27·6	2·9	3·0	13·4	64·9	
Uninsured	1·8	2·6	3·0	2·0	0·4	
Hospital type						
Private	45·9	37·3	37·7	42·4	57·6	<0·0001
NCI-designated	24·3	29·7	28·8	27·1	17·0	
Teaching	10·6	15·3	12·2	8·7	8·5	
Kaiser	16·8	15·8	19·5	19·3	13·8	
Leukapheresis						
Yes	3·5	5·3	4·7	2·5	2·6	<0·0001
No	96·5	94·7	95·3	97·5	97·4	

NCI-designated, National Cancer Institute designated cancer centre.

receiving chemotherapy, we found significant sociodemographic and age disparities in early mortality. Specifically, marital status, location of care, neighbourhood SES and health insurance type were all significantly associated with early mortality. In terms of complications, major organ dysfunction continues to be a main driver of early mortality across adult patients of all ages, although the presence of sepsis, thrombosis and leukapheresis, a poor prognostic marker, did not impact mortality when adjusted for other factors. Our study also confirms that early mortality has continued to decline across all adult AML age groups in more recent times.

Receiving care at an NCI-designated cancer centre was significantly associated with lower early mortality across all age groups compared to all other types of hospitals. This finding adds to the growing body of evidence that the setting where patients receive their cancer care affects patient outcomes (Onega *et al*, 2008, 2010). Prior studies in solid tumours have shown lower mortality and better surgical outcomes in patients treated at NCI-designated cancer centres compared to non-NCI designated facilities (Birkmeyer *et al*, 2005; Paulson *et al*, 2008; Luchtenborg *et al*, 2013). Population-based studies conducted in Los Angeles County also showed improved overall survival among adult patients with adult-onset cancers (breast, colorectal, pancreatic, gastric and lung) and adolescent and young adult patients with haematological malignancies treated at NCI-designated cancer centres (Wolfson *et al*, 2014, 2015).
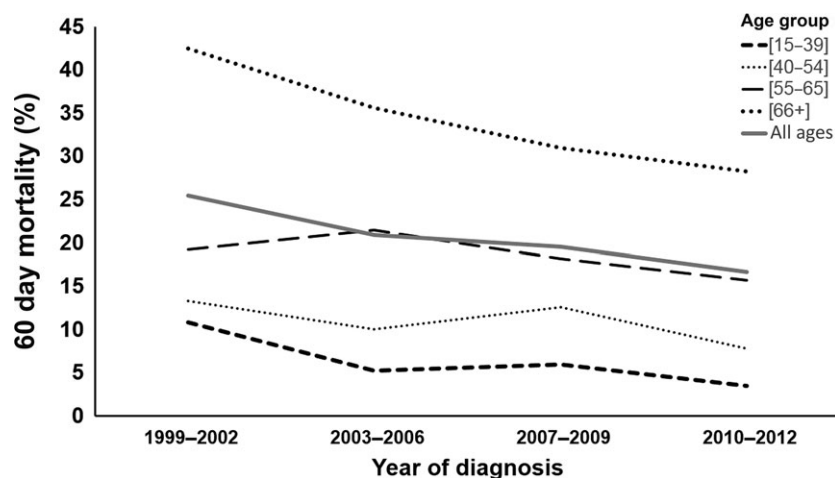
Fig 2. 60-day mortality in hospitalized acute myeloid leukaemia patients receiving chemotherapy by age (in years), in California, 1999–2012.

Table II. Complications in hospitalized acute myeloid leukaemia patients receiving chemotherapy by age at diagnosis, California, 1999–2012.

Complication	Total N = 6359 (%)	15–39 years N = 1059 (%)	40–54 years N = 1479 (%)	55–65 years N = 1556 (%)	>65 years N = 2265 (%)	P-value
Sepsis	34·6	32·2	35·8	40·6	33·2	<0·0001
Bleeding	11·9	11·0	11·5	13·4	13·9	0·044
Thrombosis	1·7	0·6	2·4	2·4	1·8	0·003
Renal failure	17·9	12·8	17·4	21·7	22·1	<0·0001
Liver failure	1·4	1·6	1·8	1·7	1·1	0·290
Respiratory failure	12·0	9·3	10·6	16·7	14·2	<0·0001
Cardiac arrest	1·7	1·0	1·9	2·2	2·0	0·140

Outcomes are thought to be better at NCI-designated cancer centres due to clinical trial availability, organizational affiliation and evidence-based cancer care (Birkmeyer et al, 2005; Bilimoria et al, 2007, 2008; Huang et al, 2014). However, few studies have evaluated how treatment at a NCI-designated cancer centre differs from other hospitals. It has been reported that NCI-designated cancer centres may have better expertise at performing a high volume of specialized care than low volume non-NCI designated facilities (Hillner et al, 2000; Bilimoria et al, 2008). Similarly, a recent study showed reduced inpatient mortality rates in AML patients treated at high versus low volume chemotherapy centres (Giri et al, 2015). The present study did not find substantial differences in the number of complications by hospital type. However, for induction therapy in AML, staff at high volume centres may be more capable of recognizing and managing complications earlier, which could improve early mortality rates. Future research should evaluate how the differences in health care delivery and access to care at a NCI-designated cancer centre leads to improved outcomes.

In this study, we also found that the type of health insurance was associated with early mortality. While our study did not observe differences in 60-day mortality between public and private health insurance, our findings that lack of health insurance was associated with 60-day mortality is consistent with a prior population-based cancer registry analysis of 19–64 year-old AML patients (Borate et al, 2015). Future research should continue to monitor the impact of health insurance on outcomes after the implementation of the Affordable Care Act (ACA) in 2014, as the ACA has resulted in a decrease in the population of uninsured (Wherry & Miller, 2016), but it is not yet clear if this results in better health outcomes.

Racial/ethnic differences have been thought to play a major role in the presentation and survival after AML. In a single-centre study, black patients more frequently presented with high-risk cytogenetics and had lower rates of clinical trial participation than whites, but the overall survival did not differ between these groups (Bierenbaum et al, 2012). In contrast, a population-based, California Cancer Registry study revealed that black AML patients had a lower odds of chemotherapy or transplant and worse long-term survival compared to non-Hispanic whites (Patel et al, 2015). Our study, however, observed a lower 60-day mortality in patients of African American race/ethnicity than non-Hispanic whites. We observed some differences in complications by race/ethnicity, but these did not follow any pattern. African Americans had higher rates of renal failure, Hispanics had higher rates of sepsis and Asians had higher rates of respiratory failure (Table SIV). The lack of any specific trend suggests that

Table III. Multivariate model of the relationship of sociodemographic and clinical factors to 60-day mortality in hospitalized acute myeloid leukaemia patients receiving chemotherapy, California 1999–2012.

Variable	Odds ratio	(95% confidence interval)	P-value
Gender			
Female versus male	0·91	(0·78, 1·06)	0·213
Age (years)			
15–39 vs. >66	0·11	(0·08, 0·16)	<0·0001
40–54 vs. >66	0·20	(0·16, 0·26)	<0·0001
55–65 vs. >66	0·32	(0·26, 0·40)	<0·0001
Race/ethnicity			
Asian versus non-Hispanic white	0·81	(0·64, 1·04)	0·094
Hispanic versus non-Hispanic white	0·82	(0·66, 1·01)	0·064
African American versus non-Hispanic white	0·66	(0·46, 0·94)	0·022
Year of diagnosis			
2003–2006 vs. 1999–2002	0·66	(0·54, 0·80)	<0·0001
2007–2009 vs. 1999–2002	0·50	(0·40, 0·61)	<0·0001
2010–2012 vs. 1999–2002	0·38	(0·30, 0·47)	<0·0001
Marital status at diagnosis			
Single marital status versus married	1·25	(1·07, 1·46)	0·006
Neighbourhood socioeconomic status			
Low versus high	1·21	(1·03, 1·41)	0·017
Health insurance status			
Medicare versus private insurance	1·07	(0·88, 1·30)	0·519
Public insurance versus private insurance	1·08	(0·81, 1·44)	0·585
Uninsured versus private insurance	2·44	(1·45, 4·13)	<0·001
Comorbidities			
1–2 comorbidities versus 0 comorbidities	1·46	(1·16, 1·84)	0·001
3+ comorbidities versus 0 comorbidities	1·97	(1·56, 2·49)	<0·0001
Bleeding versus none	1·54	(1·56, 1·88)	<0·0001
Sepsis versus none	1·05	(0·89, 1·23)	0·568
Thrombosis versus none	0·85	(0·50, 1·46)	0·563
Liver failure versus none	1·87	(1·12, 3·12)	0·017
Renal failure versus none	2·39	(2·00, 2·86)	<0·0001
Respiratory failure versus none	7·59	(6·18, 9·33)	<0·0001
Cardiac arrest versus none	15·79	(8·73, 28·56)	<0·00001
Hospital type			
Kaiser versus private	0·91	(0·73, 1·14)	0·410
NCI-designated versus private	0·45	(0·36, 0·56)	<0·0001
Teaching versus private	0·92	(0·72, 1·19)	0·536
Leukapheresis versus none	1·26	(0·85, 1·86)	0·256

NCI-designated, National Cancer Institute designated cancer centre.

Table IV. Complications in hospitalized acute myeloid leukaemia patients receiving chemotherapy by hospital type, California, 1999–2012.

Complication	Total N = 6204 (%)	Kaiser N = 1069 (%)	Teaching N = 671 (%)	Private N = 2917 (%)	NCI-designated N = 1547 (%)	P-value
Sepsis	35·6	32·1	34·7	38·2	33·3	<0·001
Bleeding	12·7	9·4	13·7	14·1	11·8	0·001
Thrombosis	1·9	1·6	1·6	1·8	2·3	0·586
Renal failure	19·2	17·9	22·5	17·5	21·9	<0·001
Liver failure	1·5	0·9	1·8	1·8	1·2	0·277
Respiratory failure	13·2	11·0	15·6	14·6	11·0	<0·001
Cardiac arrest	1·8	0·9	1·9	2·3	1·2	<0·0001

NCI-designated, National Cancer Institute designated cancer centre.

disparities in survival may not be related to initial treatment and treatment-related complications but may reflect disparities in long-term health care delivery.

In the present study, we also found that marital status and neighbourhood SES impacted early mortality in AML patients. Similar to studies that found better cancer survival among married patients (Goodwin *et al*, 1987; Aizer *et al*, 2013), we found that married patients had lower 60-day mortality, particularly among patients >65 years. There are several proposed theories underlying the beneficial effects of being married, including stronger support networks, having medical insurance, economic security and better lifestyle practices (Ayanian *et al*, 1993; Seeman, 2000; Waite & Lehrer, 2003; Manzoli *et al*, 2007; Bernstein *et al*, 2008). Our finding of higher 60-day mortality among patients residing in low SES neighbourhoods is consistent with a prior study (Hillner *et al*, 2000) and may be related to disparities in access to healthcare and more advanced disease at presentation.

We observed that major organ dysfunction and bleeding continue to be the main drivers of early mortality. We did not see significant differences across age groups, except that young patients with respiratory failure and bleeding had higher relative odds of early mortality than older patients with these complications. Further, we did not observe sepsis to be associated with early mortality, which may be a reflection of improvements in supportive care, rigorous transfusions and introduction of newer antibiotics and antifungals (Higby *et al*, 1974; Pagano *et al*, 2012; Cowan *et al*, 2015). Clinical pathways that result in increased awareness, early detection and aggressive management of respiratory failure, renal failure and bleeding may lead to improved outcomes.

Our findings are consistent with prior studies that found improvements in early mortality among AML patients over time (Othus *et al*, 2014; Percival *et al*, 2015), across all age groups, with the greatest improvement in older patients. Retrospective data showed that the 5–10% of AML patients treated on clinical trials had significant improvements in the early-mortality rate at 28 days, from 18–19% to 3–4% in one study and 20% to 12% in another study (Appelbaum *et al*, 2006; Othus *et al*, 2014). In population-based, cancer registry analyses a decrease from 18% 30-day mortality in patients treated from 1973 to 1977 to 5·8% in patients treated in 2008–2010 was seen (Percival *et al*, 2015). Our study extends these prior findings to include more recent data, showing continued improvements in early mortality, potentially due to advancements in management of infections and sepsis.

There are several limitations to this study. While we were able to identify patients that received chemotherapy while hospitalized, we did not have detailed information on the type of chemotherapy given or whether there were differences in curative *versus* palliative intent of treatment. We did not include patients who received therapy in the outpatient setting. As a result, our findings are only applicable to adult patients who receive chemotherapy requiring hospitalization.

While this comprises the majority of patients aged ≤65 years, only 40·4% of elderly patients with AML in California were hospitalized for treatment and this percentage of elderly patients hospitalized for treatment did not change substantially over the study period. Therefore, the large decline in early mortality in older patients may be reflective of healthier elderly patients who received in-patient chemotherapy for their treatment, given that elderly AML patients in general may be less likely to be offered intensive in-patient therapy due to adverse leukaemia prognostic factors and patient-related factors, including comorbidities and performance status (Othus *et al*, 2014; Medeiros *et al*, 2015; Ossenkoppele & Lowenberg, 2015). The large decline in early mortality in older patients may also be reflective of recent advances in treatment, including the use of low intensity hypomethylating agents, which have been associated with lower adverse events (Domret *et al*, 2015). Our study also lacked individual-level measures of SES to consider separately or with our neighbourhood measure. While neighbourhood and individual SES are associated, neighbourhood SES has been found to underestimate associations observed with individual-level SES (Krieger, 1992). Our study may also be subject to potential misclassification of race/ethnicity, although we previously have detected excellent overall agreement with self-reported race/ethnicity for Whites and Blacks, and good agreement for Hispanics and Asians (Gomez & Glaser, 2006; Clegg *et al*, 2007). Despite these limitations, our study includes a diverse, population-based patient population treated across all types of hospitals with findings that are more generalizable of treatment and health care delivery in the modern era than clinical trials or single institution studies.

This population-based study in adult patients with AML found a significant association between sociodemographic factors and early mortality. Being unmarried, living in a low socioeconomic neighbourhood and lacking insurance led to worse outcomes. Cancer care setting also greatly influenced outcomes, with lower early mortality observed in those treated at a NCI-designated cancer centre. We show that early mortality continues to decline across all age groups, but major organ dysfunction and bleeding continue to impact early deaths. Newer disease-directed therapies may minimally impact early mortality without more robust initiatives to prevent or mitigate these complications. Other strategies to improve outcomes include wider insurance coverage and treatment at specialty centres, where lower early mortality may result from better supportive care.

Funding sources

Conflict of Interest

The authors report no relevant conflicts of interest.

Contributions of the Authors

Concept and design: Ho, Jonas, Li, Brunson, Wun, Keegan. Acquisition and Analysis of Data: Brunson, Li, Ho, Keegan. Drafting of the manuscript: Ho, Keegan. Final approval: Brunson, Ho, Jonas, Wun, Keegan.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. ICD-9 codes of complications.

Table SII. Proportion of hospitalized acute myeloid leukemia patients hospitalized receiving chemotherapy within 30 days by age, California, 1999–2012.

Table SIII. Distribution and early mortality of hospitalized acute myeloid leukemia patients receiving chemotherapy within 30 days by WHO/FAB criteria, California, 1999–2012.

Table SIV. Complications in hospitalized acute myeloid leukemia patients receiving chemotherapy within 30 days by race/ethnicity, California, 1999–2012.

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