Patient features and survival of pediatric aplastic anemia in the USA: a large institution experience

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ABSTRACT

Background We performed the first epidemiologic investigation to examine association of demographics and clinical characteristics at diagnosis, as well as health care expense coverage, with survival of US children with aplastic anemia (AA).

Methods We obtained electronic medical record data of 1140 children aged 0–19 years diagnosed with AA followed at a pediatric health system between 2004 and 2014. Kaplan–Meier curve and Cox proportional hazards regressions were used.

Results Self-pay patients had a mortality risk five times higher than that of those insured by publicly funded insurance (hazards ratio, 95% CI: 6.0, 3.7–9.8). Other features associated with higher mortality risk include pancytopenia (hazards ratio, referent: 4.2, constitutional AA); underweight (2.0, normal-weight); platelet count $<50 \times 10^9/l$ (1.3, $\geq 50 \times 10^9/l$); male sex (1.3, female); and ages at diagnosis 6–11, 11–16 and 16–19 years (1.6, 1.9, 2.3, 1–3 years), respectively.

Conclusions Self-pay was the strongest prognostic factor for pediatric AA mortality. Older age, pancytopenia, underweight, male sex and lower platelet count were also associated with increased risk of mortality. These findings may be useful for providers, researchers and policymakers to ensure effective health care delivery to this population and to motivate future etiologic research and establishment of a surveillance registry.

Keywords blood and immune disorders, epidemiology, young people

Introduction

Aplastic anemia (AA) is a rare, life-threatening blood disorder that develops due to the failure of the bone marrow to produce enough new blood cells. Bone marrow makes stem cells that develop into red blood cells, white blood cells and platelets. At least two of the following three criteria are needed for an AA diagnosis: (i) hemoglobin level $<10 \text{ g/dl}$, (ii) absolute neutrophil count $<1.5 \times 10^9/l$ and (iii) platelet count $<50 \times 10^9/l$.¹ Severity of AA is graded according to these blood parameters along with bone marrow cellularity and reticulocyte count. AA can be acquired or inherited. Acquired AAs constitute most cases, although, in ~15–20%, the diseases are constitutional/inherited.¹ The most serious type of AA is pancytopenia, which is caused by deficiency of all three types of blood cells.¹ Identified etiologic risk factors include infections of viral origin, such as hepatitis-associated,

Epstein-Barr, parvovirus, human immunodeficiency virus, varicella zoster, measles and other viruses, as well as exposure to toxic chemicals (e.g. benzene, pesticides and insecticides) and ionizing radiation.² Yearly incidence of acquired AA in North America and Europe is between two and six cases per 1 million children. The figure is 2- to 3-fold higher in Asia.^{2,3} The incidence of childhood acquired AA peaks around ages 2–5 years and affects boys and girls to roughly the same extent.^{4,5}

Recent advances in understanding of pathogenesis, care and treatment of children with AA have led to improved long-term survival rates as high as or exceeding 90%,⁶ but outcome varies by age and severity at diagnosis, treatment

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regimen and time lag between diagnosis and treatment.⁶ Therapy for AA includes immunosuppressive therapy, hematopoietic stem cell transplantation, and supportive care.² Younger children are more responsive to therapy than older children.^{7–13} The 5-year overall survival of children with AA varies from 73 to 100% under different treatments.^{2,7} Other factors linked to survival difference include race–ethnicity, adiposity at diagnosis, AA type, blood parameters such as absolute neutrophil count and platelet count, and family socioeconomic status, as well as health care access and coverage. African American children were found to be at higher risk of mortality compared with Caucasians.¹⁴ In children with severe AA who underwent bone marrow transplantation, being overweight or underweight were associated with higher risk of mortality.¹⁵ Children with pancytopenia were at higher risk of mortality than those with constitutional AA.¹⁶ Lower absolute neutrophil count and platelet count at diagnosis were associated with increased risk of mortality.¹⁷ No substantial difference has been observed in the survival outcomes between males and females.¹⁸ Increased morbidity and worse survival rates have been considered as partially attributable to the family's socioeconomic situation, as well as inadequate health care access and coverage.^{19,20} Although abnormally low hemoglobin level and platelet count are two diagnostic criteria of AA, no study to date has examined their relationship with subsequent survival.

Most studies on AA have focused on treatment effects in a small number of patients. Reports on survival patterns by patient characteristics are scarce, perhaps because it often requires a large number of subjects for comprehensive and reliable assessment of these associations. Some findings regarding survival patterns have been reported in a few large-scale studies from Europe and Asia. In this first such study on US children, we have investigated the association of health care expense coverage, demographics, and clinical characteristics at diagnosis with overall survival in 1140 children with AA diagnosed and followed at a single institution between 2004 and 2014.^{10–12} AA is recognized by the US Social Security Administration as a severe functional impairment for affected individuals. Findings of this study could be used to inform about the disease burden and outcomes of childhood AA in the US to improve public health services for this population.

Methods

The study included children aged 0–19 years who received a diagnosis of AA and care at any clinics/hospitals within our institution between January 2004 and December 2014. Our

34 hospitals and clinics provide primary, subspecialty, inpatient and outpatient care in Delaware, Florida, New Jersey and Pennsylvania. Available data on demographics, health care expense coverage and clinical and mortality variables of 1221 children diagnosed with AA were retrieved from electronic medical records (EMR). Of these, 81 (6.6%) patients were excluded because of substantial missing information about study variables. Our Institutional Review Board approved the study protocol with a waiver for informed consent.

Study variables

Survival outcome and follow up

Overall survival status was determined by presence or absence of a death record in the EMR at the end of the study period and was coded as a binary variable. Length of follow up was defined as the duration from the date of first diagnosis to date of death, the 21st birth date, or 31 December 2014, whichever appeared first. Persons over 21 years of age could have transitioned to adult care during the study period. In addition to timing of mortality, length of follow up varied by age and year of diagnosis.

Demographic and clinical characteristics

Variables included were race–ethnicity; sex; AA type; and age, body mass index (BMI), hemoglobin level, absolute neutrophil count, and platelet count at diagnosis. Age at diagnosis was calculated as the difference between date of birth and the first date of diagnosis in years. Race–ethnicity was coded into ‘non-Hispanic African American’, ‘non-Hispanic Caucasian’, ‘Hispanic’, ‘other’ and ‘unknown’. Types of AA included constitutional AA (ICD-9 codes 284.0, 284.01, 284.09), pancytopenia (284.1, 284.11, 284.12, 284.19) and other acquired AA (284.2, 284.8, 284.81, 284.89, 284.9). The BMI at diagnosis was parameterized as age- and sex-adjusted percentiles. Serum concentrations of hemoglobin level (g/dl), absolute neutrophil count ($10^9/l$) and platelet count ($10^9/l$) at diagnosis were measured using standard assays.

Health care expense coverage

Payment sources for medical expenses were coded as ‘public’, ‘private’, ‘self-pay’ and ‘other’. Publicly funded insurance included Medicaid, Managed Medicaid and Medicare. Private payment sources included Blue Cross/Blue Shield and other types of commercial insurance. Self-pay patients included those whose medical expenses were paid entirely out of pocket at the time of AA diagnosis. Others were covered by

our institution's financial assistance program, Tricare, or other payers.

Statistical analysis

Age, BMI and blood parameters at diagnosis were categorized based on cutoffs determined from the data that best reflected their univariate association with mortality. Age at diagnosis was categorized into <1 year, 1 to <3 years, 3 to <6 years, 6 to <11 years, 11 to <16 years and 16 to <20 years. Cutoffs for BMI agreed with conventional definitions of underweight (below the fifth percentile), obesity (above the 95th percentile), and normal-to-overweight (between the 5th and 95th percentiles). Cutoffs for blood parameters were hemoglobin level, < or ≥ 8 g/dl; absolute neutrophil count, < or $\geq 0.4 \times 10^9$ /l; and platelet count, < or $\geq 50 \times 10^9$ /l.

Demographic, health care expense coverage, diagnostic and other clinical characteristics at diagnosis were summarized by survival status. The Kaplan–Meier survival curve was used to compare the proportion of post-diagnosis survival over time. Uni- and multivariable Cox proportional hazards models were used to examine the association of children's baseline characteristics at diagnosis with the risk of mortality. Hazard ratios (HR) and adjusted HRs (aHR) were presented along with associated 95% confidence intervals (CI). All tests were two-tailed with the level of significance of 5%. Statistical software SAS, version 9.3 (SAS Institute, Chicago, IL) was used for data analysis.

Results

Among 1140 children in the study, 623 (54.6%) were males and 517 (45.4%) were females. A total of 715 (62.7%) children were non-Hispanic Caucasian children, 232 (20.4%) were non-Hispanic African American, 120 (10.5%) were Hispanic and 73 (6.4%) children were in other racial-ethnic groups. There were 699 (61.3%) children diagnosed with pancytopenia, constituting the most frequently observed type of AA in the study sample, followed by 382 (33.5%) cases of acquired AA other than pancytopenia and 59 (5.2%) cases of constitutional AA. At time of diagnosis, 505 (44.3%) children had private insurance, 426 (37.4%) had publicly funded insurance, 116 (10.2%) were self-pay, and 93 (8.2%) were covered by other payers. A total of 79 (6.9%) patients were diagnosed with AA before age 1 year; 200 (17.5%), 254 (22.3%), 253 (22.2%), 256 (22.5%) and 98 (8.6%) children were diagnosed at ages 1–3, 3 to <6, 6 to <11, 11 to <16 and 16 to <19 years, respectively. Overall, 125 patients (11%) died during follow up.

Distribution of demographic and clinical characteristics is presented by survival in Table 1. Some differences were observed between these two groups. For example, mortality proportion was higher in males than in females, in non-Hispanic Caucasian and African American children than in Hispanic children, in children with pancytopenia than in other AA types, and in those with lower blood cell counts. Children insured by publicly funded insurances exhibited the best survival outcome, followed by those with private and other types of payers. Self-pay patients were on average 6.0 (95% CI: 3.8–9.6) times as likely to die compared with those with publicly funded insurance. Children diagnosed at age 1 to <3 years showed a considerable survival benefit compared with those diagnosed at other ages. In fact, there was a monotonic increasing trend of the risk of mortality over an increased age of diagnosis in patients, except for those diagnosed during infancy, so that the risk of mortality with regard to age at diagnosis followed a U-shaped curve. No substantial differences in the risk of mortality were observed between children whose BMIs were in the normal or obese ranges at diagnosis. Children with a BMI below the fifth percentile showed substantially higher risk of mortality compared with those with normal BMI, HR (95% CI): 1.8 (1.1–3.0). Kaplan–Meier curves in Figs 1 and 2 visualize the relationship between survival probability since the time of diagnosis by demographic and baseline clinical variables.

Table 2 displays the mutually adjusted associations between child characteristics at AA diagnosis and overall survival. There were no substantial differences between the univariable and multivariable results in Tables 1 and 2. In brief, children who were without public or private insurances, diagnosed with pancytopenia; underweight or obese; diagnosed at infancy or after 3 years of age; male; Caucasian; and with lower platelet count, hemoglobin level and absolute neutrophil counts had worse survival outcome. Males on average had a 27% higher risk of dying during follow up after the first AA diagnosis than their female counterparts, HR (95% CI): 1.3 (0.9–1.8). Compared with Caucasian children, African American (HR, 95% CI: 1.0, 0.6–1.5) and Hispanic (HR, 95% CI: 0.9, 0.5–1.6) children had about a 5–10% lower risk of mortality. Children with pancytopenia were 80% more likely to die than those with constitutional AA (HR, 95% CI: 0.2, 0.1–1.0), and 20% more likely to die than those diagnosed with other AAs (0.8, 0.6–1.2). Mortality risk of publicly insured children was the lowest among all payer groups. Self-pay patients had a mortality risk five times higher than that of those insured by publicly funded insurance (HR, 95% CI: 6.0, 3.7–9.8). The U-shaped risk of mortality at different ages of diagnosis evident in the univariable analysis persisted in the adjusted model.

Table 1 Distribution of clinical and demographic characteristics at diagnosis by mortality status as well as their associated hazard ratios (HRs) in pediatric aplastic anemia (AA) patients ($n = 1140$)

<i>Covariates</i>	<i>Alive/Censored (N = 1015) n (%)</i>	<i>Dead (N = 125) n (%)</i>	<i>HR^a (95% CI)</i>	<i>P-value</i>
Sex				
Female	466 (45.9)	51 (40.8)	1	—
Male	549 (54.1)	74 (59.2)	1.3 (0.9, 1.8)	0.19
Race-ethnicity				
Caucasian	637 (89.1)	78 (10.9)	1	—
African American	207 (89.2)	25 (10.8)	1.0 (0.6, 1.5)	0.82
Hispanic	108 (90.0)	12 (10.0)	0.9 (0.5, 1.6)	0.72
Other/Unknown	63 (86.3)	10 (13.7)	1.3 (0.6, 2.8)	0.49
Diagnosis				
Pancytopenia	619 (88.6)	80 (11.4)	1	—
Other AA	339 (88.7)	43 (11.3)	0.8 (0.6, 1.2)	0.24
Constitutional AA	57 (96.6)	2 (3.4)	0.2 (0.1, 1.0)	0.05
Source of health care expense coverage				
Public	393 (92.2)	33 (7.8)	1	—
Private	460 (91.1)	45 (8.9)	1.1 (0.7, 1.8)	0.60
Other	85 (91.4)	8 (8.6)	1.2 (0.6, 2.6)	0.66
Self-pay	77 (66.4)	39 (33.6)	6.0 (3.8, 9.6)	<0.0001
Age at diagnosis (years)				
<1	68 (86.1)	11 (13.9)	2.4 (1.0, 5.4)	0.04
1 to <3	189 (94.5)	11 (5.5)	1	—
3 to <6	231 (90.9)	23 (9.1)	1.5 (0.7, 3.0)	0.29
6 to <11	223 (88.1)	30 (11.9)	2.0 (1.0, 4.0)	0.05
11 to <16	219 (85.5)	37 (14.5)	2.7 (1.4, 5.2)	0.004
16 to <19	85 (86.7)	13 (13.3)	3.0 (1.3, 6.7)	0.01
Adiposity (BMI percentile) at diagnosis				
Normal ^b	795 (89.8)	90 (10.2)	1	—
Underweight ^c	98 (84.5)	18 (15.5)	1.8 (1.1, 3.0)	0.02
Obese ^d	122 (87.8)	17 (12.2)	1.1 (0.7, 1.8)	0.76
Hemoglobin level (g/dl)				
≥8	712 (89.6)	83 (10.4)	1	—
<8	126 (84.0)	24 (16.0)	1.3 (0.8, 2.1)	0.36
Absolute neutrophil count ($10^9/l$)				
≥0.38	800 (89.8)	91 (10.2)	1	—
<0.38	195 (85.9)	32 (14.1)	1.4 (1.0, 2.1)	0.08
Platelet count ($10^9/l$)				
≥50	757 (90.6)	79 (9.4)	1	—
<50	258 (84.9)	46 (15.1)	1.4 (1.0, 1.9)	0.08
Year of diagnosis				
2004–7	294 (85.2)	51 (14.8)		
2008–11	390 (87.2)	57 (12.8)		
2012–14	331 (95.1)	17 (4.9)		

^aUnivariate HRs were estimated using Cox proportional hazards model.^bNormal: >5th to <95th BMI percentile.^cUnderweight: zero–fifth BMI percentile.^dObese: ≥95th BMI percentile.

BMI, body mass index; CI, confidence interval.

Fig. 1 Kaplan-Meier curve of change in survival over time since diagnosis (years) associated with patient features of age at diagnosis, source of health care expense coverage (yes/no insurance), sex and weight status at diagnosis.

Diagnosis of AA during infancy was associated with 2.4 (95% CI: 1.0–5.4) times the risk of mortality as diagnosis at 1 to <3 years of age. Children diagnosed at 3 years of age and older had progressively worse outcomes compared with those diagnosed between 1 and <3 years, HR (95% CI) was 1.5 (0.7–3.0), 2.0 (1.0–4.0), 2.7 (1.4–5.2) and 3.0 (1.3–6.7) at age of diagnosis of 3 to <6, 6 to <11, 11 to <16 and ≥ 16 years, respectively. Both obese and underweight children had elevated risk of mortality compared with those with normal weight. Being obese at the time of diagnosis was associated with an 8% higher risk of mortality compared with normal-weight children (HR, 95% CI: 1.1, 0.7–1.8). Being underweight at the time of diagnosis was associated with significantly higher risk of mortality than normal-weight children (HR, 95% CI: 1.8, 1.1–3.0).

Discussion

Several studies around the world identified demographic and clinical characteristics at baseline as well as family socioeconomic status as prognostic factors for pediatric AA mortality. None of these studies investigated all of these factors

on a single cohort, and, to date, no such studies have been conducted on the US population. The scarce epidemiologic evidence could limit the delivery of effective services to affected children and families in the USA. In this study, we examined overall survival by demographic and clinical characteristics, as well as source of health care expense coverage, in a considerably large group of pediatric patients with AA in the USA. As in studies around the world, we observed marked variation in the risk of mortality by patient characteristics at diagnosis in our sample.

Main finding of this study

Our study reports several new findings. First, self-pay for health care coverage associated with increased mortality risk for children with AA. Reasons may include barriers to access and use of health care services and other resources necessary for effective management of AA.¹⁹ Self-pay for health care coverage may be a surrogate for adverse family socioeconomic condition. In general, self-pay patients are more likely to avoid seeking medical care unless they are faced with an emergency, or delay care until their symptoms

Fig. 2 Kaplan–Meier curve of change in survival over time since diagnosis (years) associated with clinical features (Aplastic anemia type and blood parameters) at diagnosis. *Acquired AA excluding pancytopenia.

become unbearable.^{21–23} Therefore, they are more likely to receive a diagnosis in late stages of a disease and suffer complications from aggravated medical conditions.²⁴ Moreover, obtaining referrals and medications, as well as timely, coordinated, compassionate, family-centered and culturally appropriate care are often challenging in this population.²¹ Children covered by publicly funded insurance had the lowest risk of mortality. To the best of our knowledge, this is the first report on how health care expense coverage related to mortality risk in childhood AA in the USA. Also, we identified cutoffs of hemoglobin level < 8 g/dL, absolute neutrophil count $< 0.4 \times 10^9$ /L and platelet count $< 50 \times 10^9$ /L at diagnosis to be associated with greater risk of mortality. Cutoffs of these three blood parameters are used as criteria in AA diagnosis and disease severity classification. Individuals with lower values of these three blood counts are at greater risk of mortality.^{1,17}

What is already known on this topic

The sex ratio of 1.2 in our study is identical to that reported by Jeong *et al.*¹⁹ in an investigation on 828 pediatric AA patients in

Korea. Although most studies around the world reported the same ratio of incidence as well as prevalence between male and female children with AA, a few studies from India and Pakistan showed a higher ratio of males, 2.3 and 2.9, respectively.^{25,26} The risk of mortality in males was higher in our study by 29%. In a few clinical studies that focused on treatment responses, males had a slightly worse or comparable survival outcome.^{18,27} Younger children were reported to have better survival outcomes in previous studies.^{9,18,27} In our sample, we also observed this relationship and quantified it with more finely categorized age groups. Children diagnosed between ages 1 and < 3 years demonstrated the best survival outcome in our study. Except for children diagnosed during infancy, a monotonically increased risk was observed with an increased age at diagnosis. This may be partly due to younger children having better response to both hematopoietic stem cell transplantation and immunosuppressive therapy.^{8,13,17,28} Interestingly, we observed a similar rise in risk of overall mortality with increasing age at diagnosis in children with acute lymphoblastic leukemia in a previous study. This potentially may be due to the etiologic relationship between these two hematologic disorders.^{29,30} The

Table 2 Covariate-adjusted hazard ratios (aHRs) between patient characteristics at aplastic anemia (AA) diagnosis and overall survival

Ccovariates	aHR ^a	95% CI	P-value
Sex			
Female	1	–	–
Male	1.3	0.9, 1.9	0.17
Race–ethnicity			
Caucasian	1	–	–
African American	0.9	0.6, 1.5	0.72
Hispanic	0.8	0.4, 1.5	0.49
Other/Unknown	1.0	0.4, 2.1	0.94
Diagnosis			
Pancytopenia	1	–	–
Other AA	0.7	0.5, 1.1	0.13
Constitutional AA	0.2	0.1, 1.0	0.05
Source of health care expense coverage			
Public	1	–	–
Private	1.1	0.7, 1.8	0.61
Other	1.2	0.5, 2.6	0.70
Self-pay	6.0	3.7, 9.8	<0.0001
Age at diagnosis (years)			
<1	1.9	0.8, 4.4	0.14
1 to <3	1	–	–
3 to <6	1.2	0.6, 2.4	0.65
6 to <11	1.6	0.8, 3.2	0.18
11 to <16	1.9	0.9, 3.8	0.08
16 to <19	2.3	1.0, 5.3	0.05
Adiposity (BMI percentile) at diagnosis			
Normal ^b	1	–	–
Underweight ^c	2.0	1.2, 3.3	0.01
Obese ^d	1.1	0.6, 1.9	0.68
Hemoglobin level (g/dl)			
≥8	1	–	–
<8	1.2	0.7, 2.1	0.53
Absolute neutrophil count (10 ⁹ /l)			
≥0.38	1	–	–
<0.38	1.2	0.8, 1.9	0.37
Platelet count (10 ⁹ /l)			
≥50	1	–	–
<50	1.3	0.9, 2.0	0.16

¹Covariate-aHRs were estimated using multivariable Cox proportional hazards model.

²Normal: >5th to <95th BMI percentile.

³Underweight: zero–fifth BMI percentile.

⁴Obese: ≥95th BMI percentile.

BMI, body mass index; CI, confidence interval.

proportion of constitutional AA in our study was comparable with that in the study by Jeong *et al.*¹⁹ Children with constitutional AA in our study exhibited considerably superior survival outcome compared with those with pancytopenia.¹⁹ Mortality

risk between non-Hispanic Caucasian, African American and Hispanic children was similar in our study. In a study of 1281 children with AA from around the world, Barker *et al.* reported that among race-ethnic groups, survival outcome was the worst in black children, and that high and low BMIs (BMI percentiles >75% and 5–25%, respectively), but not underweight (BMI percentile <5%), were associated with worse post-bone marrow transplantation survival in children with severe AA.¹⁵ However, we observed the worst outcome in children who were underweight at diagnosis, which was followed by a slightly elevated risk of mortality in obese children. It is possible that the different racial/ethnic findings in the study by Barker *et al.* are reflective of this different patient population. The population of the Barker *et al.* study consists of pediatric patients aged 2–19 years who underwent a first allogeneic hematopoietic stem cell transplantation for severe AA worldwide. Future studies on the relationship between weight status and pediatric AA survival are needed to advance knowledge on this topic.

What this study adds

Our study is a good first step to gather epidemiologic evidence of patient-level biological and socioeconomic characteristics at diagnosis and to present their associations with overall survival outcome in children with AA in the USA. After the simultaneous adjustment of study variables, self-pay health care coverage, pancytopenia, older age at diagnosis, underweight, male sex and lower platelet count were associated with increased risk of mortality. Of these, self-pay was the most prominent. The advancement in understanding of the association of patient features at diagnosis and the risk of pediatric AA mortality may be useful for providers, researchers, and policymakers to ensure effective health care delivery to this population, and to motivate future etiologic research as well as the establishment of a surveillance registry.

Limitations of this study

Simultaneous examination of comprehensive patient features covering demographics, AA specific clinical characteristics at diagnosis, and health care expense coverage was a major strength of this study. The use of a large sample for this investigation was another major strength as it enhances the generalizability of our findings. Being an observational study, the validity of our results may have been influenced by unmeasured confounders including treatment, supportive care, and time lapse between diagnosis and treatment to some extent. For example, we did not have adequate treatment-related information including treatment response and complications. Transition from pediatric care to adult

clinics limited follow up of children after they turned 21. This may have resulted in an underestimation of the risk of mortality.

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