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ORIGINAL ARTICLE

Incidence and treatment outcome of aplastic anemia in Taiwan—real-world data from single-institute experience and a nationwide population-based database

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Abstract

Aplastic anemia (AA) is a rare disease characterized by pancytopenia and bone marrow failure. The incidence of AA tends to be higher in Asia than in the West, but real-world data about AA in Asia remain limited. We aimed to describe the basic data, treatment, and outcome of AA patients from our institute and evaluate the incidence of AA in Taiwan with a nationwide population-based cohort from National Health Insurance Research Database (NHIRD). We identified patients older than 2 years with AA in the Registry of Catastrophic Illness of NHIRD between 2001 and 2010 and excluded patients with any diagnosis suggestive of congenital or secondary bone marrow failure. With a total of 1270 patients, the overall incidence was 5.67 per million people per year, and there was a biphasic age distribution of incidence rate, highest in ≥ 70 years (19.83 per million people per year) and another peak at age 2–9 years (5.26 per million people per year). Overall, the 5-year survival was 60.0%. Hematopoietic stem cell transplantation (HSCT) and anti-thymocyte globulin-based immunosuppressive therapy (IST) were the major first-line treatments in patients younger than 40 years and were linked with good survival. In contrast, the majority of patients older than 60 years were treated with androgen, and the survival was poor. In multivariate analysis, "severe AA," "very severe AA," and "treatment other than HSCT, IST, or androgen" were independent risk factors for inferior survival. In conclusion, the incidence of AA in Taiwan is consistent with nearby Asian countries and is higher than in the West. Advanced age is associated with higher incidence and poorer outcome.

Keywords Aplastic anemia · Epidemiology · Outcome research · Bone marrow failure

Introduction

Aplastic anemia (AA) is a rare disease characterized by pancytopenia and bone marrow failure. Complications of pancytopenia, such as infection, bleeding, and anemia, are usually the first presentations of AA. The incidence of this disease is generally below 2.5 cases per million per year in studies conducted in Europe and America [1–8]. By contrast, the incidence rates reported from Asian countries, such Thailand, China, and Malaysia, are higher [9–13]. The cause(s) of

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higher AA incidence in Asia remain(s) unclear, and environmental factors, such as exposure to drugs, toxin, or viruses, had been discussed as possible explanations for the geographic difference [9, 14–16]. Hematopoietic stem cell transplantation (HSCT) and anti-thymocyte globulin (ATG)-based immunosuppressive therapy (IST) have been the mainstay of treatment for this disease for years [17, 18]. Although the efficacy of HSCT and IST has been well documented in clinical trials, real-world data regarding incidence and treatment outcome in Asian countries remain limited. Therefore, we aimed to describe the basic data, possible etiologies, treatment, and survival from our single-institute experience and evaluate the incidence of AA in Taiwan from and a nationwide population-based healthcare database.

Methods

Database

The National Health Insurance (NHI) program of Taiwan started since 1995 and currently covers more than 99% of Taiwan population, and NHI adopted International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. The National Health Insurance Research Database (NHIRD), provided by the Bureau of NHI and maintained by National Health Research Institute, has detailed healthcare data of nearly the total Taiwan population. The NHI system has a policy of catastrophic illness certification to benefit populations with specific diseases, such as cancers, major organ failure, and inherited diseases. AA has been one of the catastrophic illnesses since the start of NHI. Once a patient is diagnosed with AA, the treating physician can apply to the Bureau of NHI with supporting data, such as hemogram and reports of bone marrow biopsy, for the certification of catastrophic illness. The application will be reviewed by experienced hematology specialists to confirm that the diagnosis is made following generally accepted diagnostic criteria. Renewal of the certification is necessary every 5 years. Therefore, we utilized the Registry of Catastrophic Illness in NHIRD to identify potential AA patients in Taiwan population.

Study populations

Two patient populations were used in this study. The NHIRD cohort consisted of patients aged 2 years or older and diagnosed as AA (ICD-9-CM code: 284) in the Registry of Catastrophic Illness of NHIRD between January 1, 2001 and December 31, 2010. To focus on acquired AA, we excluded patients with congenital AA (ICD-9-CM: 284.0), dyskeratosis congenita (ICD-9-CM: 757.39), Felty's syndrome (ICD-9-CM: 714.1), and Kostmann's syndrome (ICD-9-CM: 288.01). Patients with prior diagnosis of diseases associated with secondary pancytopenia, such as cancers (ICD-9-CM: 140-208), systemic lupus erythematosus (SLE, ICD-9-CM: 710.0), organ transplantation (ICD-9-CM: V42.0, V42.1, V42.6, V42.7, V42.81-V42.84, V42.89, V42.83, 996.81, 996.82, 996.83, 996.84, 996.85, 996.86), human immunodeficiency virus (HIV) infection (ICD-9-CM: 042), myelodysplastic syndrome (MDS, ICD-9-CM: 238.7), paroxysmal nocturnal hemoglobinuria (PNH, ICD-9-CM: 283.2), pure red cell aplasia (PRCA, ICD-9-CM: 284.8), drug-induced pancytopenia (ICD-9-CM: 284.1), or myelophthisic anemias (ICD-9-CM: 284.2), were also excluded. The date of diagnosis was defined as the date of the registration into to the Registry of Catastrophic Illness. Population data were drawn from the Department of Household Registration Affair, Ministry of Interior, Taiwan, for the calculation of overall and specific incidence rates.

Another cohort of patients was retrospectively identified from National Cheng Kung University Hospital (NCKUH) medical information database for outcome analysis and to validate the diagnostic accuracy in NHIRD cohort. Patients were included if they were diagnosed and treated for AA at the NCKUH and also be listed in the Registry of Catastrophic Illness from January 1, 2001 to December 31, 2017. Patients diagnosed between the years 2001 and 2010 were also part of the total NHIRD cohort. Patients who were younger than 2 years old, or meeting the exclusion criteria in NHIRD cohort, were excluded. Medical records and specimens of bone marrow biopsy were reviewed by one hematologist and two experienced hematopathologists retrospectively. We used widely accepted Camitta's criteria to define the diagnosis and severity of AA [18, 19]. Patients with diagnosis disagreement between hematologist and pathologists were classified as non-AA.

Study definitions

To survey for the etiologies of AA in Taiwan, NHIRD cohort patients with a diagnosis of possible etiologies in at least one admission or two outpatient visit records were identified, including hepatitis A (ICD-9-CM: 070.0, 070.1), hepatitis B (ICD-9-CM: 070.2, 070.3, V02.61), hepatitis C (ICD-9-CM: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62), hepatitis E (ICD-9-CM: 070.43, 070.53), other hepatitis (ICD-9-CM: 573.1, 573.2, 573.3, 070.6, 070.9, V02.69, V02.60), infectious mononucleosis (ICD-9-CM 075), dengue fever (ICD-9-CM 061), and pregnancy (ICD-9-CM: V22, V23, 631-679).

Records of first-line and second-line treatments were extracted from in-patient database of NHIRD. Patients receiving IST were identified by the use of ATG. If the difference between dates of HSCT and ATG use was less than 15 days, the ATG was regarded as HSCT-related medication rather than IST. Cyclosporine, erythropoietin, and androgen were not reimbursed by NHI during the study period, and patients treated with these drugs could not be identified from NHIRD. Also,

data of laboratory tests, disease severity, lifestyle, and environmental exposure were lacking in NHIRD.

In severe AA and very severe AA patients treated with IST, androgen, and eltrombopag, we defined complete response (CR) by transfusion independence, ANC > 1.5×10^9/L, and platelets > 150×10^9/L; partial response (PR) is defined by no longer meeting criteria for severe disease, but not fulfilling the criteria of CR [20]. Refractory is defined as not meeting the criteria for either PR or CR. The response in patients with early death or loss from follow-up within 3 months after treatment initiation was classified as "not evaluable."

Statistical analysis

For descriptive statistical analyses, rates and proportions were compared with χ^2 tests. The trend of incidence over time was tested with Mann-Kendall test. Kaplan-Meier method was used for estimation of survival probabilities, and a log-rank test was used to compare between survival curves. Cox proportional hazards regression was used to analyze risk factors for survival. Data manipulation and cleaning of NHIRD were performed with SAS version 9.3, and statistical analysis was carried out in software R version 3.4.0.

Results

Basic data of the NHIRD cohort

From January 1, 2001 to December 31, 2010, a total of 1646 potential cases of AA were identified from the Registry of Catastrophic Illness of NHIRD. The study population of NHIRD cohort consisted of 1270 cases after excluding 376, and the major causes of exclusions were prior history of MDS ($n = 254$), cancers ($n = 46$), congenital AA ($n = 37$), PRCA ($n = 27$), and PNH ($n = 6$) (Fig. 1). The median age at diagnosis was 48.5 years (range 2–96.7), and a total of 631 patients (49.68%) were male. Non-B, non-C hepatitis was the possible etiology in 47 patients (3.7%), as well as hepatitis C in 34 (2.7%), cytomegalovirus in 29 (2.3%), hepatitis B in 18 (1.4%), and pregnancy in 13 patients (1.0%) (Table 1).

Basic data of the NCKUH cohort

From the years 2000 to 2017, a total of 109 patients in the Registry of Catastrophic Illness with the diagnosis of AA were identified from medical information database of our institute. Eleven patients were excluded due to a history of cancer ($n = 5$), age < 2 years ($n = 2$), end-stage renal disease (ESRD) ($n = 1$), PRCA (n = 1), PNH ($n = 1$), and history of organ transplantation ($n = 1$). Another 11 patients were excluded because of unavailability of bone marrow biopsy specimens (diagnosed at other hospitals) or treatment information. Among the remaining 87 patients, the diagnosis of 3 patients was changed to hypocellular MDS after reviewing medical records and bone marrow slides, producing a positive predictive rate of 0.966. The positive predictive rate among patients diagnosed in 2001–2010 (part of the total NHIRD cohort) was 0.948 (55 out of 58). Compared with the NHIRD cohort, the NCKUH cohort had a higher proportion of pediatric patients (31.0% vs. 17.4%, $p < 0.01$) and a younger median age of diagnosis (37.3 vs. 48.5 years) (Table 1). Possible etiologies of AA can be spotted in 19 patients (22.4%), including hepatitis B in 7 (8.3%), drug in 5 (6.0%), HCV in 5 (6.0%), and unknown

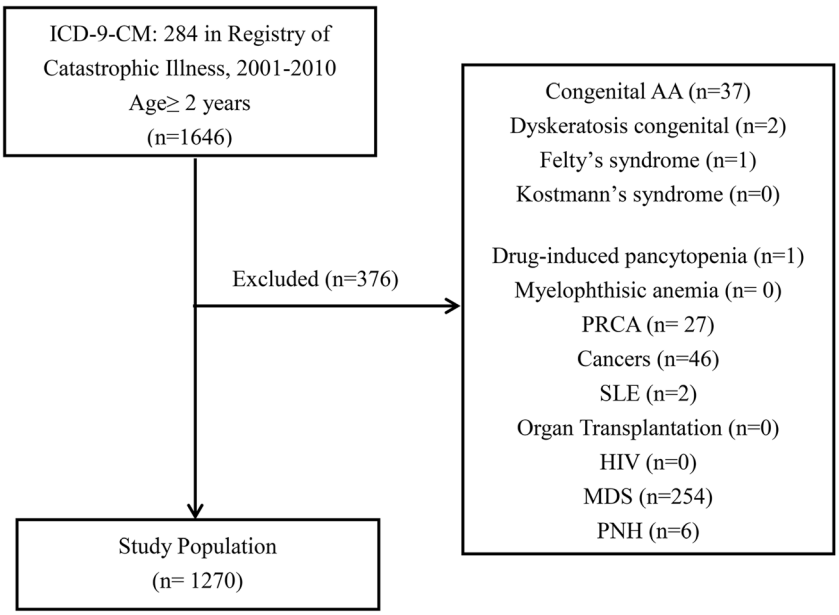

Fig. 1 Patient inclusion and exclusion algorithm. AA aplastic anemia, PRCA pure red cell aplasia, SLE systemic lupus erythematosus, HIV human immunodeficiency virus, MDS myelodysplastic syndrome, PNH paroxysmal nocturnal hemoglobinuria

Table 1 Patient demographics. Abbreviations: *CMV*, cytomegalovirus infection; *EBV*, Epstein-Barr virus infection; *IST*, immunosuppressive therapy; *ATG*, anti-thymocyte globulin; *HSCT*, hematopoietic stem cell transplantation

	NHIRD cohort ($n = 1270$)	NCKUH cohort 2000–2017 ($n = 84$)
Male gender, no. (%)	631 (49.7)	39 (46.4)
Median age at diagnosis, years (range)	48.5 (2.0–96.7)	37.3 (2.01–89.6)
Pediatric patients, no. (%)	221 (17.4)	26 (31.0)*
Possible etiologies, no. (%)		
Hepatitis A	0 (0.0)	0 (0)
Hepatitis B	18 (1.4)	7 (8.3)**
Hepatitis C	34 (2.7)	5 (6.0)**
Hepatitis E	0 (0.0)	0 (0.0)
Other hepatitis	47 (3.7)	4 (4.8)
Infectious mononucleosis	1 (0.1)	0 (0.0)
Dengue	0 (0.0)	0 (0.0)
Pregnancy	13 (1.0)	0 (0.0)
Drug	NA	5 (6.0)
Severity, no. (%)		
Non-severe	NA	31 (36.9)
Severe	NA	44 (52.4)
Very severe	NA	9 (10.7)
First-line therapy, no. (%)		
Allogeneic HSCT	82 (6.5)	10 (11.9)
IST	387 (30.5)	32 (38.1)
Rabbit ATG	298 (77.0)	13 (40.6)
Horse ATG	89 (23.0)	18 (56.2)
Unknown	0 (0)	1 (1.2)
Androgen	NA	24 (28.6)
Best supportive care	NA	17 (20.2)
Eltrombopag	NA	1 (1.2)
Unknown	801 (63.0)	0 (0)
Salvage therapy, no.	105 (8.0)	20 (24.0)
Allogeneic HSCT	33	10
Sibling	NA	2
Matched unrelated	NA	5
Mismatched unrelated	NA	3
Second IST	72	7
Eltrombopag	NA	4
Androgen	NA	3

*$p < 0.01$

**Two patients had co-infection of hepatitis B and C

hepatitis in 4 (4.8%). Severe, very severe, and non-severe patients consisted of 44 (52.4%), 9 (10.7%), and 31 cases (36.4%), respectively (Table 1). Bone marrow karyotyping was available in 50 patients, and five of them had cytogenetic abnormalities, including del(Y) in two patients and inv(Y)(p11.2q11.23), del(X), and trisomy 8 in one patient each.

Evaluation of AA incidence in Taiwan

Estimated from 1270 AA cases during 223,860,241 person-years, the estimated overall incidence of AA in Taiwan was 5.67 per million people per year (95% confidence interval [CI] 5.37–5.99) (Table 2). No trends of change in incidence rates over time were detected ($\tau = -0.315$, $p = 0.243$) (Fig. 2a). The sex-specific incidence rates in male and female were 5.56 and 5.79, with a ratio of 0.96 (95% CI 0.86–1.07) (Table 3). The difference between male- and female- specific incidence rates was insignificant ($p = 0.505$). We observed biphasic age distribution of incidence rate, highest in ≥ 70 years (19.83 per million people per year) and another peak at age 2–9 years (5.26 per million people per year) (Fig. 2b).

Treatment

As for first-line treatment in the NHIRD cohort, 82 patients (6.5%) were treated with allogeneic HSCT, and 387 (30.5%) received ATG-based IST. The remaining 63% patients had no identifiable anti-AA treatments. These patients might have received treatments that were not reimbursed by National Health Insurance (such as cyclosporine alone, androgen, or erythropoietin), or best supportive care only. In patients ≥ 60 years old, only 11 (2.3%) received allogeneic HSCT, and 51 (10.8%) received IST. Rabbit ATG and horse ATG were used in 298 (77%) and 89 (23%) patients, respectively. Of these IST-treated patients, 105 (27.1%) had records of more than one line of treatment, including 33 s-line HSCT and 72 s IST (Table 1).

Among 84 NCKUH cohort patients, allogeneic HSCT, ATG-based IST, and androgen were the front-line treatment in 10 (11.9%), 32 (38.1%), and 24 (28.6%) patients, respectively. One (1.2%) patient was treated initially with eltrombopag, and 17 (20.2%) received supportive care only (including transfusion, G-CSF, and erythropoietin) (Table 1). Among severe and very severe AA patients, those who were less than 40 years old were mainly treated with HSCT and IST, while older patients were more frequently treated with androgen or best supportive care (Supplement Fig. 1).

Response to front-line ATG-based IST can be evaluated in 94% (30/32) patients, and the best attained response at any time was CR in 10 (33%), PR in 7 (23%), and refractory in 13 (43%) (response not available in 2 because of early death). In 24 patients treated with androgen at front line, a response was observed in 10 out of 21 evaluable patients. Second IST was given to seven refractory patients, and PR is only observed in one. Allogeneic HSCT was the salvage treatments for refractory or relapsed disease in 10 patients. Donors of stem cells were matched sibling in two, matched unrelated in five, and mismatched unrelated in three. Among four patients who received eltrombopag for refractory disease, two (50%) experienced complete (CR) and one (25%) experienced partial recovery (PR) of hemogram at the dose of 50 mg per day.

Table 2 Standardized incidence of aplastic anemia by year of diagnosis

	Year										
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
Male											
N. of cases	55	76	94	54	65	64	40	60	62	61	631
Incidence	4.93	6.77	8.34	4.77	5.73	5.62	3.51	5.25	5.42	5.33	5.56
Female											
N. of cases	78	94	74	50	60	64	48	49	53	69	639
Incidence	6.95	8.70	6.81	4.57	5.45	5.77	4.30	4.37	4.69	6.07	5.79
Total											
N. of cases	133	170	168	104	125	128	88	109	115	130	1270
Incidence	6.09	7.72	7.59	4.67	5.59	5.70	3.90	4.81	5.06	5.70	5.67

Annual incidence expressed in case/million inhabitants

Survival

The median time of follow-up was 2.56 years (range 0–10.9) and 3.57 years (range 0–17.6) in NHIRD and NCKUH cohorts, respectively. Overall survivals of all patients in NHIRD and NCKUH cohorts were 83.0% (95% CI 80.9–85.1) and 90.1% (95% CI 83.8–96.9) at 6 months, 76.3% (95% CI 73.9–78.7) and 86.1% (95% CI 78.7–94.1) at 1 year, 68.5% (95% CI 65.9–71.2) and 83.2% (95% CI 75.3–92.0) at 2 years, and 75.3% (95% CI 65.9–86.1) and 60.0% (95% CI 57.1–63.0) at 5 years after diagnosis (Fig. 3a, b). When grouped by age, NHIRD cohort patients with age 2–19 years had 84.4% (95% CI

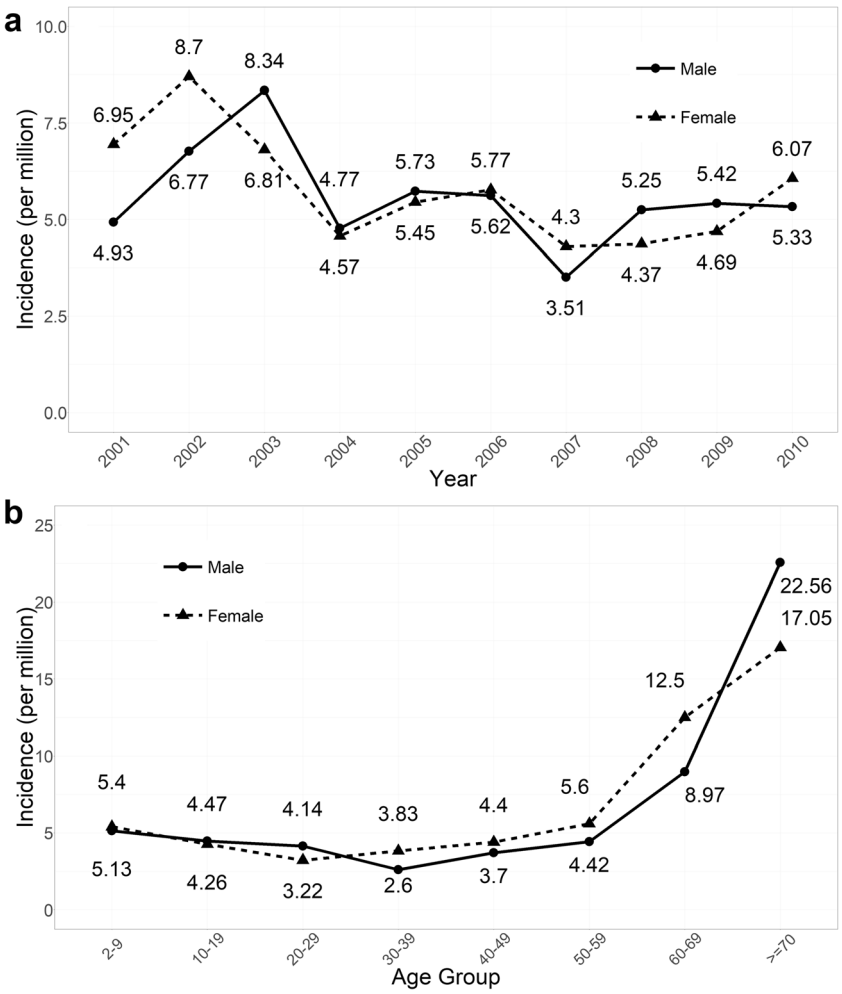

Fig. 2 **a** Sex-specific incidence by year of diagnosis. **b** Sex-specific incidence by different age groups

Table 3 Standardized incidence of aplastic anemia by gender and age

	Age at diagnosis (years)								
	2–9	10–19	20–29	30–39	40–49	50–59	60–69	> 70	Total
Male									
N. of cases	58	75	79	49	69	60	67	174	631
Incidence	5.13	4.47	4.14	2.60	3.70	4.42	8.97	22.56	5.56
Female									
N. of cases	56	66	59	71	81	77	100	129	639
Incidence	5.40	4.26	3.22	3.83	4.40	5.60	12.50	17.05	5.79
Total									
N. of cases	114	141	138	120	150	137	167	303	1270
Incidence	5.26	4.37	3.69	3.21	4.04	5.01	10.79	19.83	5.67

Annual incidence expressed in case/million inhabitants

79.7–89.4%) 5-year survival rate, and the survival rate dropped to 75.1% (95% CI 69.7–80.9%) in 20–39 years, 60.9% (95% CI 55.0–67.4%) in 40–59 years, and 38% (95% CI 33.6–43.4%) in ≥ 60 years age groups. ($p < 0.001$; Fig. 3c). With patients of age 2–19 years as a reference, those of age 20–39, 40–59, and ≥ 60 years had hazard ratios (HR) of 1.71, 3.28, and 5.71, respectively ($p < 0.05$ in all groups; Table 4). Patients aged ≥ 60 years in NCKUH cohort also had a worse outcome compared with younger ones ($p = 0.027$) (Fig. 3d; Table 5). Female patients had a trend toward worse 5-year survival than male in the NHIRD cohort (62.4% vs. 57.6%, HR 1.18) ($p = 0.059$), but not in the NCKUH cohort (71.6% vs. 78.5%, HR 0.70) ($p = 0.42$) (Fig. 3e, f).

In the NHIRD cohort, there was no significant difference in 5-year survival rate between patients treated with IST (68.8%, 95% CI 64.0–73.9%) or HSCT (68.4%, 95% CI 58.5–79.8%) ($p = 0.48$) at first-line, and both were higher than patients received other treatments ($p < 0.01$) (Fig. 3g). In the NCKUH cohort, patients treated with front-line allogeneic HSCT had a 100% survival at 5 years, compared with 76%, 78%, and 55% in patients treated with IST, androgen, and other treatments ($p = 0.03$) (Fig. 3h).

Patients in the NCKUH cohort with very severe AA had a worse outcome than non-severe AA (HR = 4.36, $p = 0.03$) (Fig. 4a; Table 5). An excellent 5-year survival (100%) is observed in patients who achieved CR after front-line IST, in contrast to 53.8% in those who were IST-refractory ($p = 0.02$) (Fig. 4b). Multivariate analysis of the NCKUH cohort showed that "severe AA," "very severe AA," and "others" treatment were independent risk factors for inferior survival (Table 5).

In NHIRD cohort, patients younger than 20 years old and treated with first-line HSCT had 86.1% 5-year survival rate (95% CI 72.7–100.0%), which was significantly better than 61.7% (95% CI 50.0–76.3%) from patients older than 20 years ($p = 0.02$) (Fig. 4c). Age remained to be a substantial factor of survival in patients treated with first-line IST ($p < 0.01$) (Fig. 4d). Comparing two different types of ATG in first-line use, patients treated with horse ATG had better 5-year overall survival (75.2%, 95% CI 66.8–84.8%) than those treated with rabbit ATG (66.4%, 95% CI 60.7–72.6%) ($p = 0.03$) (Fig. 4e).

Discussion

The incidence rates of AA reported from Europe, North America, and South America are around two cases per million inhabitants per year, whereas the incidence is much higher in Asian countries [1–3, 6, 7, 9–12, 21]. In this study, we estimated the incidence and survival rates of AA patients diagnosed between 2001 and 2010 in Taiwan with a large nationwide population-based healthcare database. The incidence of AA in Taiwan during the study period is 5.67 per million inhabitants per year and is in accordance with the incidence of 3.7–5.0 in Thailand; 4.8 in Malaysia; 3.3 in Shanghai, China; and 5.16 from pediatric AA patients in Korea [9, 11, 12, 22]. We found that there was no difference in the sex-specific incidence of AA, which is in agreement with the several population-based studies, including a recent study from Sweden [3, 7, 8]. The male predominance reported in Thailand and Malaysia is not observed in our study, which may reflect the difference in environment or occupation exposure [9, 12].

Fig. 3 Overall survival of **a** all patients with aplastic anemia in NHIRD cohort, **b** all patients in NCKUH cohort, **c** patients of different age group in NHIRD cohort, **d** patients of different age group in NCKUH cohort, **e** patients of different gender in NHIRD cohort, **f** patients of different gender in NCKUH cohort, **g** patients grouped with first-line treatment in NHIRD cohort, and **h** patients grouped with first-line treatment in NCKUH cohort. IST immunosuppressive therapy, HSCT hematopoietic stem cell transplantation

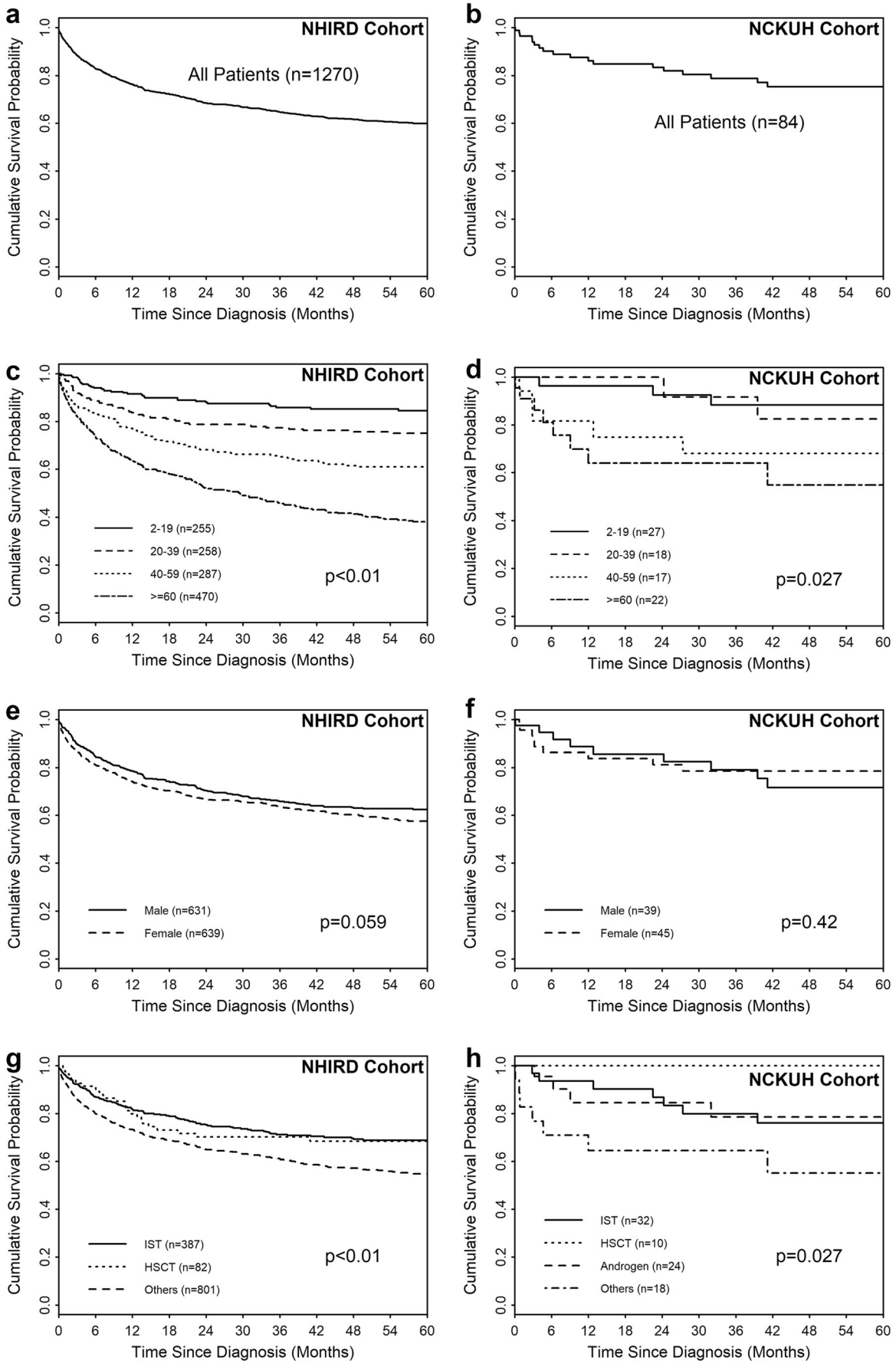
a
NHIRD Cohort
All Patients (n=1270)
b
NCKUH Cohort
All Patients (n=84)
c
NHIRD Cohort
2-19 (n=255)
20-39 (n=258)
40-59 (n=287)
>=60 (n=470)
p<0.01
d
NCKUH Cohort
2-19 (n=27)
20-39 (n=18)
40-59 (n=17)
>=60 (n=22)
p=0.027
e
NHIRD Cohort
Male (n=631)
Female (n=639)
p=0.059
f
NCKUH Cohort
Male (n=39)
Female (n=45)
p=0.42
g
NHIRD Cohort
IST (n=387)
HSCT (n=82)
Others (n=801)
p<0.01
h
NCKUH Cohort
IST (n=32)
HSCT (n=10)
Androgen (n=24)
Others (n=18)
p=0.027
Cumulative Survival Probability
Time Since Diagnosis (Months)

Table 4 Univariate Cox regression of NHIRD cohort. *IST*, immunosuppressive therapy; *HSCT*, hematopoietic stem cell transplantation

	Hazard ratio	95% Confidence interval	*p* value
Age (years)			
2–19	1*		
20–39	1.71	1.13–2.57	0.010
40–59	3.28	2.26–4.76	< 0.001
≥ 60	5.71	4.06–8.06	< 0.001
First-line treatment			
IST	1*		
HSCT	1.16	0.77–1.75	0.481
Others	1.63	1.32–2.01	< 0.001
Gender			
Male	1*		
Female	1.19	0.99–1.42	0.059

*Reference category

Studies using registry or healthcare database are often questioned by the diagnostic accuracy of the study population. A recent study from Spain showed that the diagnosis of AA could be validated in only 15% patients selected by ICD codes from hospital discharge data and mortality registry [23]. Patients in the NHIRD cohort of this study were identified from the Registry of Catastrophic Illness and exclusion of patients with any diagnosis suggesting congenital or secondary bone marrow failure. The accuracy of such an approach was validated by reviewing bone marrow slides and medical record of patients from our institute (the NCKUH cohort). Although some differences of basic characteristics exist between the two cohorts, the diagnosis of AA could be confirmed in 96.6% (84/87) patients. The younger median age of diagnosis and the higher proportion of pediatric patients in the NCKUH cohort reflect the nature that younger patients are more likely to be referred to a transplant-eligible center. Therefore, although we could not examine all patients in the NHIRD cohort, we believed the diagnosis of AA was reliable in the vast majority.

Consistent with other studies [1, 7–9, 24, 25], there is a biphasic pattern in the age distribution of incidence, with one peak observed in patients below 10 years old and the other in the elderlies. MDS is a major etiology of cytopenia in the elderlies and the diagnosis largely depends on the presence of dysplastic morphology in bone marrow. However, it is often difficult to distinguish hypocellular MDS from AA by morphology in a severely hypocellular bone marrow. Hypocellular MDS and AA are similar in some features, and the border between them is further obscured by the discovery of increased prevalence of clonal hematopoiesis in older AA patients [26]. Age-related clonal hematopoiesis can also be observed in patients with refractory cytopenia but no definite evidence of MDS, a condition so-called idiopathic cytopenias of undetermined significance (ICUS) [27]. Therefore, a subset of older AA patients may have co-existing MDS or ICUS and are different from

Table 5 Univariate and multivariate Cox-regression of the NCKUH cohort. *IST*, immunosuppressive therapy; *HSCT*, hematopoietic stem cell transplantation

	Univariate			Multivariate		
	Hazard ratio	95% Confidence interval	*p* value	Hazard ratio	95% Confidence interval	*p* value
Age (years)						
2–19	1*			1*		
20–39	0.93	0.17–5.09	0.9	1.09	0.18–6.59	0.926
40–59	2.58	0.69–9.63	0.158	1.18	0.25–5.64	0.832
≥ 60	4.32	1.32–14.14	0.016	3.50	0.62–19.86	0.156
First-line treatment						
IST	1*			1*		
HSCT	< 0.01	0–infinity	0.997	< 0.01	0–infinity	0.997
Androgen	0.81	0.24–2.70	0.733	0.40	0.30–7.45	0.624
Others	2.42	0.90–6.45	0.078	2.63	2.22–85.90	0.005
Severity						
Non-severe	1*			1*		
Severe	1.59	0.55–4.57	0.393	14.45	3.03–68.81	0.001
Very severe	4.36	1.16–16.36	0.029	120.5	12.83–1131.71	< 0.001
Gender						
Male	1*			1*		
Female	0.69	0.29–1.68	0.423	0.36	0.13–1.07	0.066

*Reference category

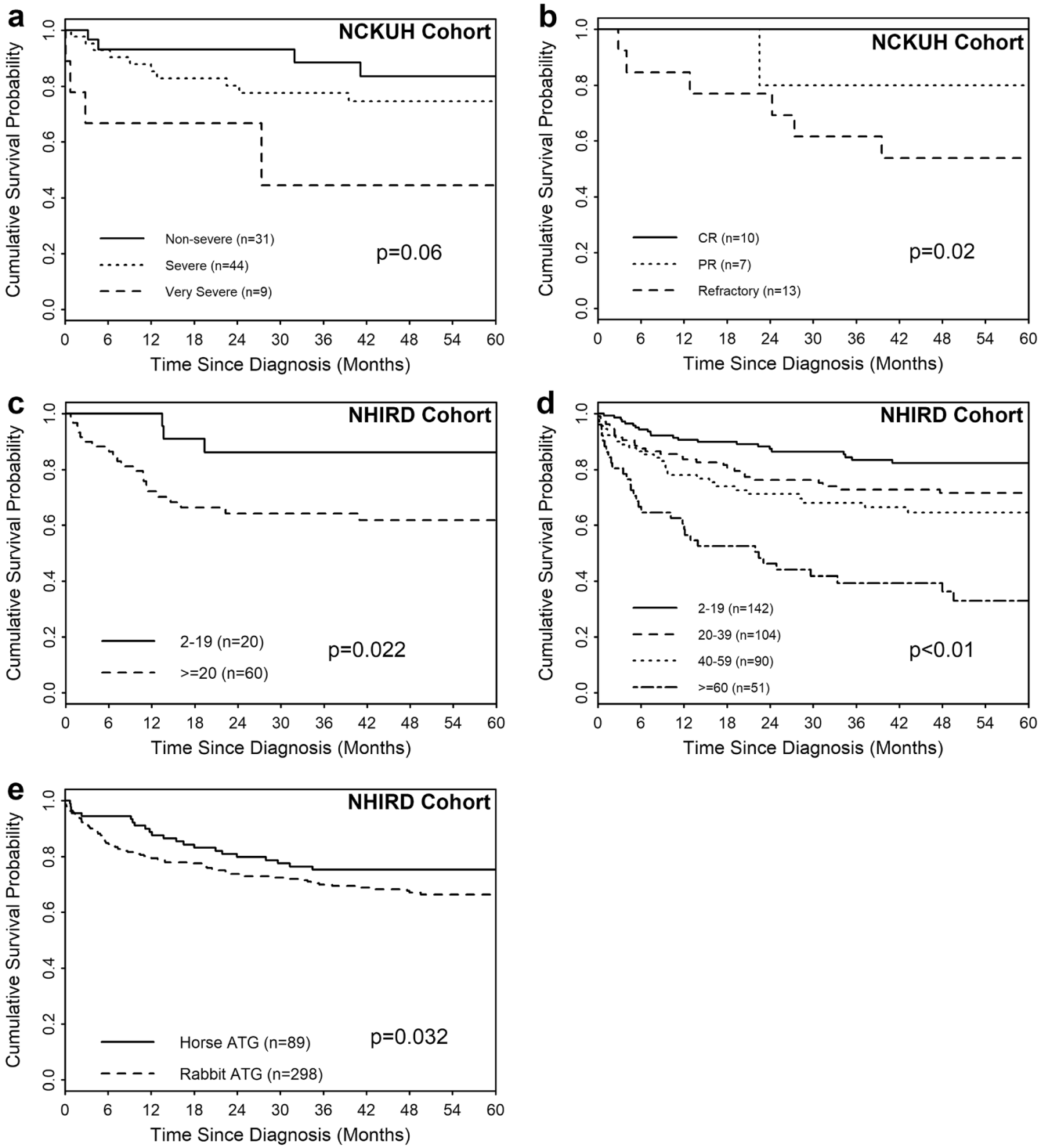

Fig. 4 **a** The effect of disease severity on overall survival in all patients of NCKUH cohort. **b** Overall survival of patients receiving first-line immunosuppressive therapy in NCKUH cohort grouped by response. **c** Overall survival of patients receiving first-line hematopoietic stem cell transplantation in NHIRD cohort grouped by age. **d** Patients receiving first-line immunosuppressive therapy in NHIRD cohort grouped by age. **e** The effect of different types of anti-thymocyte globulin among patients received first-line immunosuppressive therapy in NHIRD cohort. CR complete response, PR partial response, ATG anti-thymocyte globulin

younger patients in the pathogenesis [28, 29]. The growing understanding of clonal hematopoiesis may help in the differentiation between these overlapping syndromes.

An early study reported high frequency (23.9%) of post-hepatitic AA in children in Taiwan, and the higher prevalence of hepatitis viruses had been discussed to be the cause of

higher incidence rate in Asia [14]. In our study, a diagnosis of non-B, non-C hepatitis could be identified in 47 (3.7%) NHIRD cohort patients and 4 (4.8%) NCKUH cohort patients within 1 year before the diagnosis of AA. We also recognized a history of hepatitis B and C in 18 (1.4%) and 34 (2.7%) patients. The frequency is much lower than previously reported and may be explained by universal newborn hepatitis B vaccination policy since 1984 in Taiwan [14, 30]. Although we could not establish the causation between hepatitis and AA in these patients, the data is consistent with early observations that 4–10% patients had a history of hepatitis in the Far East [31]. The difference of genetic background and environment exposure between Western and Asian countries may also be responsible for higher AA incidence rate in Asia. However, this data is not available in NHIRD.

In the NHIRD cohort, only 37% patients received first-line therapy with either HSCT or IST. This data is lower than reported in two population-based studies from Spain and Sweden [7, 8]. However, since cyclosporine, erythropoietin, and androgen were not reimbursed by National Health Insurance during the study period, we could not identify patients receiving non-ATG therapy in NHIRD. Therefore, the others group was a mixture of patients treated with non-ATG immunosuppressive therapy or androgens, and patients who did not, or did not need to receive treatment (such as patients with non-severe AA). Although NHIRD is limited by lack of severity data, we observed 36.9% non-severe disease in the NCKUH cohort. The proportion of non-severe AA is similar to a study in Korean children, as well as a recent report from Sweden, but higher than in the paper from Spain [7, 8, 11]. Data from NCKUH cohort also revealed a high proportion of older AA patients treated with androgen or supportive care at first line. Therefore, the low rate of patients treated with HSCT or IST in NHIRD cohort is likely due to a higher proportion of non-severe cases, and non-ATG therapy, especially in older patients.

In accordance with prior studies, age is a strong predictor of survival, in patient subgroups treated with either first-line HSCT or IST in our study [7, 8]. Overall, the outcome of patients of age 2–19 years was good with 84.4% 5-year survival rate, in contrast to 38% in patients older than 60 years. The prognosis of older patients with AA is uniformly poor in most studies. In NHIRD cohort, only 2.3 and 10.8% of patients ≥ 60 years old received HSCT and IST. Among patients with severe or very severe AA in NCKUH cohort, only one patient (11%) was treated with ATG-based IST (Fig. 3). A recent study also found a relatively large proportion of patients were treated with cyclosporine alone in patients ≥ 60 years old [8]. These findings reflect that physicians refrain from HSCT and ATG in older patients, probably due to higher toxicity of treatment and more inferior physical condition. Eltrombopag, a synthetic thrombopoietin receptor agonist with promising efficacy in aplastic anemia either alone or in combination with IST, is well tolerated [32–34]. Despite the low number, three out of four patients treated with salvage eltrombopag experienced response, including two CR. Therefore, utilization of eltrombopag in the treatment of AA could potentially improve the outcome, especially in older patients.

In conclusion, the incidence of AA in Taiwan is consistent with nearby Asian countries, which is higher than in the West. Advanced age and severe disease are linked with inferior outcome. More studies are needed to improve the treatment and outcome in elderly patients with AA.

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Compliance with ethical standards

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (NCKUH-B-ER-103-282). For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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