Aplastic Anemia and Risk of Incident Atrial Fibrillation — A Nationwide Cohort Study —

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Background: This retrospective cohort study sought to follow up patients with aplastic anemia (AA) to evaluate their risk of developing atrial fibrillation (AF).

Methods and Results: From the National Health Insurance Research Database of Taiwan, this study identified an AA cohort (n=3,921), a general population cohort (n=17,617,843) and a propensity score-matched none AA cohort (PSM non-AA cohort in brief, n=15,684) in 2000–2010. By the end of 2011, the incident AF was higher in the AA cohort than in the general population and PSM non-AA cohorts (8.94 vs. 1.14 and 6.47 per 1,000 person-years, respectively). The adjusted hazards ratio of AF for the AA cohort was 2.12 (95% confidence interval 1.46–3.08) compared with the PSM non-AA cohort, after controlling for covariates. However, after further controlling for the competing risk of death, adjusted subhazard ratio was 1.21 (95% CI 0.97–1.50). Among those who developed AF, the AA cohort had a higher mortality rate (83.7 vs. 51.1 per 100), but a lower rate of incident stroke (26.0 vs. 41.5 per 100), compared with the PSM non-AA cohort.

Conclusions: Patients with AA could have an elevated risk for AF. The mortality risk increased further for those who develop AF.

Key Words: Aplastic anemia; Atrial fibrillation; Cohort study

Aplastic anemia (AA) is a rare disorder that manifests as an inability of hematopoietic stem cells to produce mature blood cells. Patients with AA usually present with symptoms associated with pancytopenia; namely anemia, thrombocytopenia and leukopenia. The pathogenic mechanism underlying AA is complex and has not been well defined. Recent emerging evidence proposes that inflammation might play a crucial role in the development of AA.

The burden of atrial fibrillation (AF) in developing and developed countries is rapidly increasing, with great concern because of the associated high morbidity and mortality. Several risk factors for AF development have been proposed and among them, inflammation has recently attracted the attention of research. To the best of our knowledge, there has not been an investigation of an association between AA and the risk of AF development. Hence, the present study sought to use Taiwan insurance data to establish propensity score-matched (PSM) cohorts for evaluating whether patients with AA are at a risk of developing AF, in addition to a comparison with general population controls.
Patients diagnosed with AF (ICD-9-CM 427.31) at baseline, aged less than 18 years, or with incomplete information on demographic data were excluded from all cohorts. All cohorts were followed up until subjects received a new diagnosis of AF, died or withdrew from the NHI program, or until December 31, 2011.

Statistical Analysis
Distributions of sex, age, and comorbidities were compared between the AA cohort and general population cohort and tested using Chi-square for categorical variables and t-test for continuous variables. Comparisons between the AA cohort and the PSM non-AA cohort were tested using the standardized difference: ≤0.10 indicated a negligible difference.

We used the Kaplan-Meier method to measure the cumulative incident AF for the 3 study cohorts. The log-rank test examined differences between the AA and general population cohorts, and between the AA and PSM non-AA cohorts. We further measured the cumulative incident AF for the AA and PSM non-AA cohorts, incorporating competing risk in the model using the Aalen-Johansen estimator. Overall incidence rates of AF (per 1,000 person-years) were calculated for the 3 cohorts, and by covariates between.
Results

This study consisted of 3,921 patients in the AA cohort, 17,617,843 persons in the general population cohort, and 15,684 persons in the PSM non-AA cohort (Table 1). Compared with the general population cohort, the AA cohort was much older, had more men, and comorbidities, CHA2DS2-VASc scores and CHADS2 scores were more prevalent. The AA and PSM non-AA cohorts were similar in their distributions of sex, age and most comorbidities. Figure 2A shows that the cumulative incidence of new-onset AF was 4.6% higher in the AA cohort than in the general population (log-rank test P<0.001). The overall incidence density rate of AF was more than 8-fold greater in the AA cohort than in the general population, with an aHR of 1.62 (95% CI 1.34–1.97) after adjusting for age, sex, and the comorbidities (Table 2). The adjusted sHR was 1.77 (95% CI 1.46–2.14) after further controlling for death.

The mean follow-up period was shorter in the AA cohort than in the PSM non-AA cohort (2.97 (SD 3.29) vs. 5.44 (SD 3.30) years), with the cumulative incidence of AF being 2.5% greater in the AA cohort after 6-year follow-up (Figure 2B).
Table 2. Incidence Density Rates and Hazard Ratios of AF for Aplastic Anemia Cohort vs. General Population Cohort

| Aplastic anemia | No (n=17,617,843) | Yes (n=3,921) |
|-----------------|------------------|---------------|
| AF              |                  |               |
| Event           | 129,342          | 104           |
| Person-years    | 113,108,088      | 11,637        |
| Rate*           | 1.14             | 8.94          |
| Crude HR (95% CI)| 1 (Ref.)         | 8.10 (6.69, 9.81)***** |
| Adjusted HR† (95% CI) | 1 (Ref.)       | 1.62 (1.34, 1.97)***** |
| Crude sHR (95% CI) | 1 (Ref.)        | 2.80 (2.31, 3.40)***** |
| Adjusted sHR† (95% CI) | 1 (Ref.)    | 1.77 (1.46, 2.14)***** |

**P<0.001. †Multivariable analysis including age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, CAD, COPD, PAOD, CKD, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, pregnancy, and stroke (death was also added in the model to measure adjusted sHR). *Incidence rate, per 1,000 person-years. AF, atrial fibrillation; HR, hazard ratio; sHR, subhazard ratio. Other abbreviations as in Table 1.

**Figure 2.** Kaplan-Meier graphs of cumulative incident atrial fibrillation (AF) in the AA cohort compared with the general population cohort (A), with the propensity score-matched (PSM) non-AA cohort (B) and with the PSM non-AA cohort after controlling for death (C).
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The overall incidence density of AF was 1.4-fold greater in the AA cohort than in the PSM non-AA cohort (8.94 vs. 6.47 per 1,000 person-years) (Table 3). The AA cohort to PSM non-AA cohort aHR was 2.12 (95% CI 1.46–3.08, P<0.001). Results also showed that the incident AF was elevated for men, the elderly and those with comorbidity. Most cases of new-onset AF occurred in the 7 years of follow-up, more in the AA cohort than in the PSM non-AA cohort (99/104 vs. 473/552). Our further data analysis showed that the AA cohort to PSM non-AA cohort

### Table 3. Incidence Density of AF and Multivariate Analysis Estimated Aplastic Anemia Cohort aHR by Sex, Age, Comorbidity and Follow-up Period and asHR Further Controlling for Deaths

| Aplastic anemia | No | Yes |
|-----------------|----|-----|
|                 | Event | PY | Rate^a | Event | PY | Rate^a | aHR (95% CI)^† | asHR (95% CI)^† |
| **All**         | 552  | 85,306 | 6.47 | 104  | 11,637 | 8.94 | 2.12 | (1.46, 3.08)***** | (0.97, 1.50) |
| **Sex**         |     |     |     |     |     |     |     |     |     |
| Female          | 291  | 54,230 | 5.37 | 45  | 6,235 | 7.22 | 1.46 | (0.68, 3.13) | 0.94 | (0.59, 1.51) |
| Male            | 261  | 31,076 | 8.40 | 59  | 5,402 | 10.9 | 2.63 | (1.16, 5.93) | 1.40 | (0.87, 2.25) |
| P for interaction | 0.51 |     |     |     |     |     |     |     |     |
| **Age strata, years** |     |     |     |     |     |     |     |     |     |
| 18–64           | 62  | 48,044 | 2.93 | 12  | 7,237 | 4.65 | 1.33 | (0.30, 5.96) | 1.40 | (0.62, 3.19) |
| ≥65             | 490  | 37,262 | 13.2 | 92  | 4,400 | 20.9 | 2.14 | (1.38, 3.32)***** | 1.19 | (0.92, 1.55) |
| P for interaction | 0.43 |     |     |     |     |     |     |     |     |
| **Comorbidity‡** |     |     |     |     |     |     |     |     |     |
| No              | 78  | 31,685 | 2.46 | 17  | 5,402 | 3.15 | 3.00 | (0.31, 28.8) | 3.00 | (0.50, 18.0) |
| Yes             | 474  | 53,621 | 8.84 | 87  | 6,236 | 14.0 | 2.00 | (1.33, 3.00)***** | 1.11 | (0.87, 1.41) |
| P for interaction | 0.88 |     |     |     |     |     |     |     |     |
| **Follow-up period, years** |     |     |     |     |     |     |     |     |     |
| ≤7              | 473  | 72,958 | 6.48 | 99  | 10,299 | 9.61 | 2.15 | (1.48, 3.13)***** | 1.34 | (0.96, 1.68)^* |
| >7              | 79  | 12,349 | 6.40 | 5  | 1,338 | 3.74 | 1.00 | (0.06, 16.0) | 1.00 | (0.14, 7.10) |

*P<0.05, **P<0.001. ^Incidence rate, per 1,000 person-years. †Multivariable analysis including age, sex, and comorbidities; further controlling for death to estimate asHR. ‡Patients with any one of these comorbidities: hypertension, diabetes mellitus, hyperlipidemia, CAD, COPD, PAOD, CKD, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, pregnancy and stroke. aHR, adjusted hazard ratio; asHR, adjusted subhazard ratio. Other abbreviations as in Tables 1,2.

### Table 4. Mortality and Stroke Rates for Those Who Developed AF Compared Between the Aplastic Anemia Cohort and Propensity Score-Matched None Aplastic Anemia Cohort

| Aplastic anemia | No | Yes |
|-----------------|----|-----|
| **AF (n)** | 552 | 104 |
| **Death (n)** | 282 | 87 |
| Mortality rate (%) | 51.1 | 83.7 |
| Mean followed time ± SD (years) | 2.05±2.19 | 1.20±1.39 |
| Crude HR (95% CI) | 1 (Ref.) | 2.38 (1.87, 3.04)***** |
| Adjusted HR^† (95% CI) | 1 (Ref.) | 2.50 (1.94, 3.23)***** |
| **Stroke (n)** | 229 | 27 |
| Stroke rate (%) | 41.5 | 26.0 |
| Mean followed time ± SD (years) | 1.76±2.07 | 1.19±1.48 |
| Crude sHR (95% CI) | 1 (Ref.) | 0.73 (0.36, 1.46) |
| Adjusted sHR^† (95% CI) | 1 (Ref.) | 0.73 (0.36, 1.48) |

^*P<0.001. †Multivariable analysis including sex, age, comorbidities of hypertension, diabetes mellitus, hyperlipidemia, CAD, COPD, PAOD, CKD, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, pregnancy and stroke; (death was also added in the model to measure adjusted sHR). CI, confidence interval. Other abbreviations as in Tables 1,2.
adjusted sHR was 1.21 (95% CI 0.97–1.50) after controlling for death. 

Figure 2C shows that the cumulative incidence probability of developing AF was somewhat alike for the AA and PSM non-AA cohorts, after accounting for death as the competing risk. Table 4 shows, among those who developed AF, the AA cohort had a greater mortality rate than the PSM non-AA cohort (83.7% vs. 51.1%, or 87/104 vs. 282/552), with an aHR of 2.50 (95% CI 1.94–3.23) for the AA cohort, after a shorter follow-up. The incidence of stroke among AF cases was slightly lower in the AA cohort than in the PSM non-AA cohort, with an adjusted sHR of 0.73 (95% CI 0.36–1.48).

Discussion

This population-base retrospective cohort study demonstrated an increased risk of new-onset AF in patients with AA. The risk is greater for men than for women and greater for the elderly than for the younger. Most of the AF cases occurred during the early follow-up period, ≤ 5 years. Our findings are in accordance with current knowledge that male sex and advanced age play an important role in the development of AF. In addition, the risk of developing AF is greater in subgroups with comorbidity, implying that comorbidity may enhance the AF risk for AA patients. This relationship was no longer significant once we accounted for the competing risk for death, compared with the PSM non-AA cohort. Our observation indicated that patients with AA may be etiologically at increased risk of AF but, because of their higher mortality risk, their actual incidence of AF is not very different from that of non-AA individuals.

Previous studies have documented the role of immune-mediated inflammation-induced bone marrow destruction in the development of AA. In patients with AA, pro-inflammatory cytokines such as interleukin-6 and tumor-necrosis factor-α can affect the renal production of erythropoietin and erythroid colony-forming bone marrow erythroid progenitors. The role of the inflammatory response in the initiation and perpetuation of AF has been well established. Inflammation associated with AA might be strongly linked to the development of cardiovascular disorders and infections. Both AA and AF involve reactive oxygen species generation. Thus, the provoked inflammation could link AA to the initiation of AF, but it is unclear if this is a direct link. Perhaps, inflammation (and/or sympathovagal imbalance) because of AA might be strongly linked in advance to the development of cardiovascular disorders or infection, resulting in subsequent AF initiation indirectly.

The proportional cumulative incidence of AF in the AA cohort was approximately 5% greater than in the general population in the 12 years of follow-up, and 2.5% greater than in the PSM non-AA cohort. Most cases of AF occurred in 5–6 years. It is important to note that AF patients in the AA cohort were at high risk of death. Near 84% of the AF patients in the AA cohort died soon after AF developed, with an sHR of 2.50 for death relative to AF patients in the PSM non-AA cohort. With the strong competing risk of death, the AA cohort was, therefore, less likely to develop stroke, particularly in survivors. The sHR of developing AF for the AA cohort was moderately greater than that for the PSM non-AA cohort after controlling for the competing risk of death, but not significant. Therefore, the cumulative incidence curves of AF were parallel for the 2 cohorts, consistently with a little difference (Figure 2C).

The management of patients with AA and later with AF is of great importance. However, the administration of anticoagulant drugs to these patients is somewhat challenging. The risk of bleeding complications because of the pancytopenia, including severe anemia and thrombocytopenia in AA patients, is of concern. The optimal strategy for the use of anticoagulants in AA patients complicated with AF remains unclear.

Strengths and Limitations

One of the strengths of this study is that we established the study cohorts using the Taiwan NHIRD, which has been documented as data with high quality and validity. First, the study population was monitored for an adequate period with minimal loss to follow-up. Finally, we used propensity score-matching to establish a comparison cohort and applied competing risk analysis to minimize the bias.

There are also some limitations to our study. First, the diagnostic accuracy of AA, AF, and other comorbidities using ICD codes in the database is probably a major limitation of the current study. Second, this nationwide dataset did not provide detailed personal lifestyle data, such as cigarette smoking, alcohol use and physical activity. Third, the detailed assessments of AA stage, pancytopenia degree, and hemoglobin or reticulocyte levels were unavailable for further evaluation of the variation in AF risk. Finally, we cannot exclude the possibility of an underestimation of AF incidence.

Conclusions

This study is the first to demonstrate that patients with AA have an elevated risk of developing AF. An extremely high risk of death from AF in AA patients was observed soon after AF developed. It seems important to monitor patients with AA to prevent complications and those who develop AF to prevent premature death. Further research is also required to explore the detailed mechanism for the relationship between AA and AF development.

Disclosures

None.

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