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New-onset Atrial Fibrillation is Associated With Polycystic Kidney Disease

A Nationwide Population-based Cohort Study

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Abstract: Cardiovascular complications remain the major problems contributing to morbidity and mortality in patients with polycystic kidney disease (PKD).

Therefore, the authors hypothesized that atrial fibrillation (AF) is closely associated with PKD. The authors conducted a nationwide population-based cohort study to investigate the risk of AF in patients with PKD.

Using data from inpatient claims, the authors enrolled 7203 patients aged over 20 years who were diagnosed with PKD from 1998 to 2010 with no history of AF as the PKD cohort. They randomly selected 28,739 people without PKD as controls and frequency matched them with patients with PKD according to their age, sex, and baseline comorbidity.

In total, 247 PKD patients were diagnosed with AF, representing an incidence of 7.08 per 1000 person-years, whereas 807 cases of AF occurred in the comparison cohort, yielding an incidence of 4.98 per 1000 person-y, with an adjusted HR (aHR) of 1.31 (95% CI = 1.14–1.51). The risk of AF increased from an aHR of 1.59 (95% CI = 1.15–2.21) to 3.64 (95% CI = 1.93–6.85) when the number of risk factors increased from 1 to more than 5 in comparison with patients without risk factors.

A remarkably high incidence rate and risk was observed in patients with PKD when multiple risk factors were combined. A high index of suspicion should be maintained when examining PKD patients with irregular betas. Early prophylactic therapy is warranted in these patients.

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Abbreviations: AF = atrial fibrillation, aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PKD = polycystic kidney disease.

INTRODUCTION

Atrial fibrillation (AF) is the most clinically prevalent arrhythmia and frequently associates with severe cardiovascular complications.[1] Atrial arrhythmogenic remodeling has been suggested to play a fundamental role in mediating the development of atrial arrhythmia, which refers to any change in atrial structure and function and can originate from a variety of cardiac diseases and conditions.[2] The mechanisms involved in AF are complex and include structural remodeling, autonomic nervous system changes, and abnormal changes in Ca^{2+} handling.[1–4] First, structural remodeling presents as atrial enlargement; tissue fibrosis has been assumed to be closely associated with the development of persistent AF; and atrial dimensions have been assumed as a key determinant of persistent AF.[5] Second, the activation of the autonomic nervous system is suggested to be closely associated with the initiation and maintenance of AF, and adrenergic activation may enhance I_{CaL}, ryanodine receptor 2 subtype (RyR2) open probability, and SR Ca^{2+} load.[6,7] Finally, accumulating evidence has indicated that intracellular Ca^{2+} metabolic disorders may contribute to the induction and activation of profibrillatory remodeling through Ca^{2+} cell-related signal pathways.[8]

Polycystic kidney disease (PKD) is a prevalent genetic disorder and autosomal dominant polycystic kidney disease (ADPKD) is the most common disease, occurring in approximately 1 in 500 people.[9] Mutations of *PKD1* account for 85% of ADPKD cases, and mutations of *PKD2* account for 15%; *PKD1* and *PKD2* encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively.[9] Although PKD typically manifests with renal cysts, extrarenal manifestations, particularly in cardiovascular abnormalities, are occasionally observed. Cardiovascular complications remain the major problems contributing to morbidity and mortality in patients with PKD. Left

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ventricular hypertrophy, mitral valve prolapse, and aortic aneurysm are occasionally observed in patients with PKD.[10–13] Accumulating evidence has revealed that the enlargement of renal cysts inevitably activates the renin–angiotensin–aldosterone system (RASS) and sympathetic activity in both circulating and intra-renal cyst.[14] A previous study identified all of the major components of the renin–angiotensin–aldosterone system in ADPKD kidneys, including angiotensinogen, angiotensin II, renin, ACE, and angiotensin receptors.[14] Enhanced sympathetic activity has also been observed in ADPKD. A remarkably higher plasma concentration of norepinephrine and epinephrine was noted in patients with essential hypertension, with or without renal failure.[15] In addition, idiopathic dilated cardiomyopathy (IDCM) characterized by dilated ventricle and attenuated systolic function is found to be associated with polycystic kidney disease.[16] Idiopathic dilated cardiomyopathy was reported to be more prevalent in human ADPKD patients than in the general population, particularly in cases with *PKD2* mutations, with an approximately 200-fold increased prevalence.[16]

Considering activation of the RAAS and the sympathetic system, as well as the remarkably high incidence of left ventricular hypertrophy, mitral valvular prolapse, and IDCM in patients with PKD, we hypothesized that AF is closely associated with PKD. Data regarding the relationship between AF and PKD has been lacking until now. We conducted a nationwide population-based cohort study to investigate the risk of AF in patients with PKD.

MATERIALS AND METHODS

Data Source

We designed this study as a population-based retrospective cohort study based on the National Health Insurance Research Database (NHIRD). The NHIRD contains all claims data from the Taiwan National Health Insurance (NHI) program, which is a single-payer compulsory insurance program that was established in 1995. The Taiwan NHI covered nearly 99.9% of the 23 million residents of Taiwan in 2014. For this study, we used a subset of the NHIRD-containing health care data, including files of inpatient claims and the registry of beneficiaries. The National Health Research Institutes encrypted the original identification information and assigned anonymous identification numbers to protect patient privacy before releasing the database for research. This study was approved by the Ethics Review Board at China Medical University (CMUH104-REC2–115). Disease status was recorded according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Study Patients

To investigate the association between the risk of AF and PKD, we constructed a PKD cohort and a comparison cohort (as shown in the Supplemental Figure 1, http://links.lww.com/MD/A656). The PKD cohort comprised patients aged older than 20 years with PKD (ICD-9-CM 753.12 and 753.13), identified from inpatient claims from 1998 to 2011. The index date of the PKD patients was the date of the first diagnosis for PKD. The comparison cohort comprised patients in the NHIRD without PKD, frequency matched by age (in 5-y bands), sex, and baseline comorbidity of hypertension (ICD-9-CM 401–405), chronic obstructive pulmonary disease (COPD) (ICD-9-CM 491, 492, and 496), congestive heart failure (ICD-9-CM 428), diabetes (ICD-9-CM 250), chronic kidney disease (ICD-9-CM-585), hyperlipidemia (ICD-9-CM 272), and stroke (ICD-9-CM 430–438) at a ratio of 1:4. The index date of the comparison patients was the same year as that of the matched cases, with a randomly assigned month and day. Patients in both cohorts diagnosed with AF (ICD-9-CM 427.31) at the baseline were excluded. Overall, 7203 PKD patients and 28,739 comparison patients were followed-up until a diagnosis of AF, loss to follow-up, death, withdrawal from the NHI program, or the end of 2011.

Statistical Analysis

Distributions of age ($\leq$49 y, 50–64 y, and $\geq$65 y), sex, and comorbidities were compared between the PKD and comparison cohorts, and examined using the χ^2 test. The median (interquartile range, IQR) ages and follow-up times of both cohorts were measured and compared using a Mann–Whitney *U* test. The cumulative incidence curves of AF were estimated using the Kaplan–Meier method and log-rank test. The overall and sex-, age-, comorbidity-, and follow-up time-specific incidence density rates (per 1000 person-y) were calculated for both cohorts. The identification of death events was based on hospital discharge because of death and withdrawal from the NHI as indicated in the NHIRD. After accounting for the competing risks of death, the PKD-to-comparison-cohort subhazard ratio (SHR) and the 95% confidence intervals (CIs) for AF were estimated using univariable and multivariable competing-risks regression models. The multivariable models were concurrently adjusted forage, and the comorbidities of hypertension, COPD, congestive heart failure, diabetes, chronic kidney disease, hyperlipidemia, and stroke. Further data analysis was conducted to evaluate the joint effect of PKD and AF-associated risk factors on the risk of AF. A logistic regression analysis was conducted to calculate and compare the odds ratios (ORs) of 30-day mortality from AF in the PKD cohort compared with the non-PKD cohort. Data management and statistical analysis were performed using SAS 9.3 software (SAS Institute, Cary, NC). The significance level was set at a 2-sided *P* value of less than .05.

RESULTS

Table 1 displays the demographic characteristics and comorbidities of the PKD and comparison cohorts. The majority of the patients were aged $\geq$65 years (39.2%) and more than half were women (approximately 58%). The median age was 58.7 years in the PKD cohort and 58.5 years in the comparison cohort. Comorbidities at the baseline were similar in the PKD cohort than in the comparison cohort. The median duration of follow-up was 3.96 (IQR = 1.53–7.56) years in the PKD cohort and 4.96 (IQR = 2.21–8.71) years in the comparison cohort. The Kaplan–Meier graph illustrates that the cumulative incidence of AF was significantly higher in the PKD cohort than in the comparison cohort (log-rank test, $P < 0.001$) (supplemental Figure 2, http://links.lww.com/MD/A656).

In total, 247 PKD patients were diagnosed with AF, representing an incidence of 7.08 per 1000 person-years, whereas 807 cases of AF occurred in the comparison cohort, yielding an incidence of 4.98 per 1000 person-y, with an adjusted SHR (aSHR) of 1.31 (95% CI = 1.14–1.51) (Table 2). The overall incidence and risk of AF were compared in the PKD cohort and the comparison cohort regarding the variables of sex, age, comorbidity, and follow-up time. A relatively higher risk of AF was observed in those men (aSHR = 1.38; 95% CI = 1.16–1.64), those with elder age, between 50 and 64 years (aSHR = 2.33; 95% CI = 1.72–3.17) and without comorbidity (aSHR = 1.46; 95%

TABLE 1. Characteristics of Patients Between Patients With Polycystic Kidney Disease and Patients Without Polycystic Kidney Disease

	Polycystic Kidney Disease				
	Yes (N = 7203)		No (N = 28,739)		
	n	%	n	%	*P* Value
Age, y					0.99
20–49	2312	32.1	9223	32.1	
50–64	2065	28.7	8246	28.7	
≥65	2826	39.2	11,270	39.2	
Median (IQR)*	58.7	(46.7–72.8)	58.5	(45.8–72.2)	0.54
Sex					0.94
Female	3006	41.7	12,007	41.8	
Male	4197	58.3	16,732	58.2	
Comorbidity					
Hypertension	2163	30.0	8606	30.0	0.89
COPD	421	5.84	1640	5.71	0.65
Congestive heart failure	331	4.60	1279	4.45	0.60
Diabetes	627	8.70	2486	8.65	0.88
Chronic kidney disease	1106	15.4	4352	15.1	0.65
Hyperlipidemia	322	4.47	1246	4.34	0.62
Stroke	831	11.5	3288	11.4	0.82

χ^2 test. COPD = chronic obstructive pulmonary, disease IQR = interquartile range.
* Mann–Whitney *U* test.

TABLE 2. Incidence of Atrial Fibrillation Stratified by Demographic Characteristics, Comorbidity, and Follow-up Time and Competing Risk (Death) Model Measured Subhazard Ratios for Patients With Polycystic Kidney Disease Compared With Those Without Polycystic Kidney Disease

	Polycystic Kidney Disease							
	Yes			No				
Variable	Event	PY	Rate#	Event	PY	Rate#	Crude SHR † (95% CI)	Adjusted SHR‡ (95% CI)
All	247	34,900	7.08	807	161,984	4.98	1.27 (1.11, 1.46)***	1.31 (1.14, 1.51)***
Sex								
Female	83	15,902	5.22	288	71,469	4.03	1.14 (0.90, 1.44)	1.16 (0.92, 1.48)
Male	164	18,997	8.63	519	90,515	5.73	1.35 (1.14, 1.60)***	1.38 (1.16, 1.64)***
Age, y								
20–49	18	13,863	1.30	40	57,762	0.69	1.34 (0.79, 2.27)	1.32 (0.77, 2.24)
50–64	62	10,700	5.79	119	49,115	2.42	2.31 (1.71, 3.14)***	2.33 (1.72, 3.17)***
≥65	167	10,338	16.2	648	55,107	11.8	1.36 (1.15, 1.61)***	1.36 (1.15, 1.62)***
Comorbidity§								
No	101	22,987	4.39	260	10,4348	2.49	1.44 (1.16, 1.80)**	1.46 (1.17, 1.82)***
Yes	146	11,913	12.3	547	57,636	9.49	1.20 (1.00, 1.43)*	1.21 (1.01, 1.45)*
Follow time, y								
≤1	66	6453	10.2	132	26,901	4.91	1.66 (1.25, 2.20)***	1.74 (1.31, 2.31)***
>1	181	28,447	6.36	675	135,083	5.00	1.19 (1.01, 1.39)*	1.22 (1.04, 1.43)*

CI = confidence interval, PY = person-years.
# Rate = incidence rate per 1000 person-years.
† Crude SHR, relative subhazard ratio.
‡ Adjusted SHR, subhazard ratio adjusted for age, and comorbidities of hypertension, COPD, congestive heart failure, diabetes, chronic kidney disease, hyperlipidemia, and stroke.
§ Comorbidity: patients with any one of the comorbidities (including hypertension, COPD, congestive heart failure, diabetes, chronic kidney disease, hyperlipidemia, and stroke) were classified as the comorbidity group.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

TABLE 3. Risk of Atrial Fibrillation in Polycystic Kidney Disease Patients With Different Number of Risk Factors

Number of Risk Factors	N	No. of Events	Rate*	Adjusted SHR†	95% CI
0	4058	101	4.39	1	(Reference)
1	1238	57	10.5	1.59	(1.15, 2.21)**
2	972	36	9.91	1.30	(0.88, 1.92)
3	538	26	14.3	1.67	(1.08, 2.59)*
4	265	16	21.2	2.16	(1.26, 3.68)**
5+	132	11	39.6	3.64	(1.93, 6.85)**

CI = confidence interval, SHR = subhazard ratio.
* Rate = incidence rate per 1000 person-year.
*$P<0.05$
**$P<0.01$
† Adjusted SHR: multivariable analysis, including age and sex.

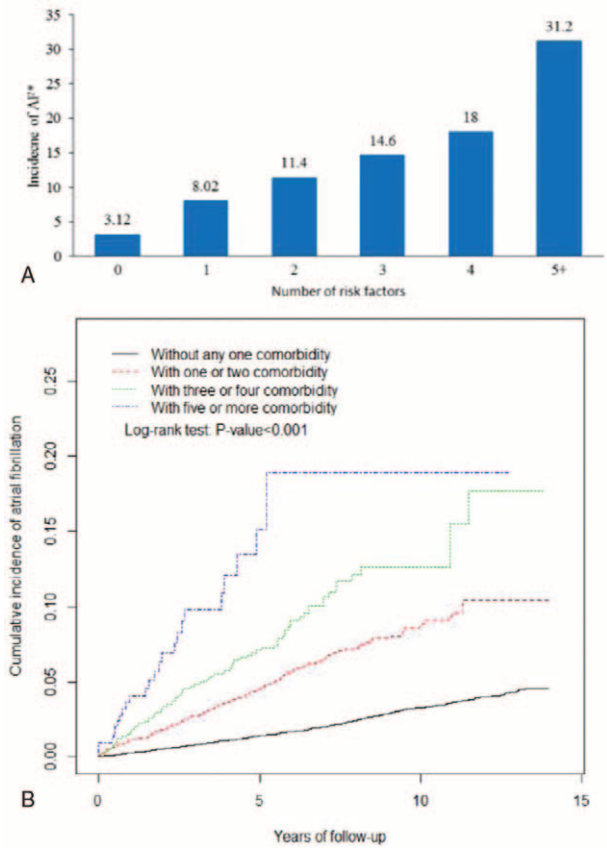

FIGURE 1. Incidence and cumulative event of new-onset atrial fibrillation (AF) in polycystic kidney disease patients with multiple risk factors. A, The incidence of AF continuously increased in patients with multiple risk factors. B, Patients were stratified into 7 groups based on the number of risk factors they had. The cumulative incidence curve with log-rank test showed that patients with more risk factors had a higher rate of new-onset AF. *Number of new-onset AF per 1000 person-years of follow-up. AF = atrial fibrillation.

TABLE 4. Odds Ratio of Mortality After Atrial Fibrillation Between Patients With Polycystic Kidney Disease and Without Polycystic Kidney Disease

	Polycystic Kidney Disease	
	No n/N	Yes n/N
Death/ACS	412/807	143/247
Rate, %	51.1	57.9
cOR (95% CI)	1 (Reference)	1.32 (0.99, 1.76)
aOR (95% CI)*	1 (Reference)	1.69 (1.24, 2.31)**

ACS = acute coronary syndrome, CI = confidence interval, OR = odds ratio.
* Multivariable analysis including age, and comorbidities of hypertension, COPD, congestive heart failure, diabetes, chronic kidney disease, hyperlipidemia, and stroke.
**$P<0.01$

CI = 1.17–1.82). The aSHR of AF in patients with PKD was significantly higher than that of the comparison cohort in the first follow-up year (aSHR = 1.74; 95% CI = 1.31–2.31).

The aSHR of AF development increased 1.03-fold for every 1-year increase in age (95% CI = 1.02–1.03). The risk of developing AF was higher for patients with the comorbidities of hypertension (aSHR = 1.50; 95% CI = 1.31–1.73), COPD (aSHR = 1.34; 95% CI = 1.09–1.63), congestive heart failure (aSHR = 2.79; 95% CI = 2.30–3.37), and chronic kidney disease (aSHR = 1.25; 95% CI = 1.07–1.46) (supplemental Table 1, http://links.lww.com/MD/A656).

Polycystic kidney disease patients with congestive heart failure and chronic kidney disease exhibited the highest aSHR of 6.09 (95% CI = 1.94–19.1), followed by PKD patients with hypertension, and congestive heart failure at 5.76 (95% CI = 3.30–10.1), and PKD patients with hypertension, congestive heart failure, and chronic kidney disease at 5.32 (95% CI = 2.71–10.4) (supplemental Table 2, http://links.lww.com/MD/A656). The incidence of AF increased with the number of risk factors. The risk of AF increased from an aSHR of 1.59 (95% CI = 1.15–2.21) to 3.64 (95% CI = 1.93–6.85) when the number of risk factors increased from 1 to more than 5 in comparison with patients without risk factors (Table 3; Figure 1). Mortality from AF in patients with PKD was higher than that in the comparison cohort (Table 4; OR = 1.69; 95% CI = 1.24–2.31).

DISCUSSION

In the current study, we observed a significantly higher incidence rate of AF (7.08 per 1000 persons-y) in patients with PKD compared with patients without PKD, which has never been reported until now. After adjustment for the confounding factors of sex, age, and comorbidities, a 1.31-fold increased risk of AF was significantly associated with PKD patients. We further determined the AF risk regarding age, sex, and comorbidities. Our results showed a higher risk of AF in cases in particular with middle age (50–64 y) and those without any comorbidity, suggesting that the development of AF in patients with PKD is highly associated with the disease itself.

In a previous study, investigating the prevalence of cardiovascular events in patients with ADPKD, Helal et al first observed a high prevalence of cardiovascular risk factors,

including hypertension, obesity, diabetes, and hypercholesterolemia, in ADPKD patients.[17,18] Notably, arrhythmia was the most prevalent self-reported cardiovascular event, occurring in approximately 25.9% of the 419 patients, followed by valvular heart disease; however, the reasons remain to be determined in the previous study.

For patients with PKD, several potential factors have been suggested to be associated with the development of AF, including IDCM,[16] overactivation of the RAAS,[14] autonomic function,[19] and abnormal calcium handling conditions.[20,21] The current study is the first to provide clinical evidence of the association between AF and PKD.

Accumulating evidence has shown that cardiac function is directly linked to calcium-dependent contraction in cardiomyocytes and cardiac dysfunction is closely associated with the mutation of calcium handling proteins.[22,23] For example, disordered intracellular calcium release channels, such as RyR2, may result in spontaneous leak of calcium from RyR2, consequently leading to arrhythmogenesis.[24,25] Recently, Anyatonwu et al suggested that mutation of PC2 leads to the calcium alternans associated with RyR2 dysfunction and may be associated with the condition of arrythmia.[24] Polycystin-2 has been regarded as an intracellular calcium channel that inhibits RyR2 expression,[24,25] alters intracellular Ca2+ signaling, and is a key contributor to AF-maintaining substrates.[8]

In addition, previous experimental data have shown that the defects of PC2 may be associated with altered calcium signaling, desensitized calcium-contraction coupling in cardiomyocytes, and abnormal changes in intracellular calcium.[21] Moreover, attenuated sensitivity to calcium in myofilaments has been suggested to be associated with the subtle diastolic dysfunction and IDCM in patients with PKD, which has been considered to be independent of the effect of hypertension and chronic renal failure.[10,16] Young normotensive ADPKD patients have been found to be associated with the development of biventricular diastolic dysfunction, which may further support the assumption.[26] In addition, PC2 deficiency has been suggested to be associated with changes in the beta-adrenergic signaling pathway. Therefore, defects in polycystin are closely associated with the remodeling of the heart in PKD patients, particularly in the absence of renal failure and high blood pressure.[21]

Collectively, our findings suggest that the abnormal calcium handling caused by the deficiency of PC2 is associated with the risk of AF in patients with PKD.

We also determined other risk factors for AF in the PKD cohort. We observed that congestive heart failure, hypertension, and age were independent risk factors associated with the development of AF in the patients with PKD. Furthermore, a graded trend of AF risk was noted in the PKD patients when the number of risk factors increased in the PKD patients. The incidence rate of AF was 4.39 per 1000 person-years for the PKD patients without comorbidities and significantly increased to 39.6 per 1000 person-years for patients with 5 or more comorbidities, who exhibited an approximately 3.64-fold increase in AF prevalence compared with those without any comorbidity. Previous studies have shown that several crucial risk factors are associated with new-onset AF, including advanced age, hypertension, and congestive heart failure. Most of these factors can result in the electrical and structural remodeling of the heart chamber and may contribute to the development and maintenance of AF.[27] In our study, these factors were more prevalent in the patients with PKD; therefore, the risk stratification of AF incidence can assist clinicians in identifying patients at a high risk of developing AF. The congenital defects of patients with PKD and the most prevalent risk factors for AF may account for the findings of the current study.

In addition, a 1.69-fold increased risk of mortality was significantly associated with AF in the PKD cohort. Previous studies have revealed that AF may cause a variety of complications and mortality in the general population and our findings showed a consistent effect of AF on mortality in PKD patients.

The strengths of our study are its population-based design, generalizability of findings, and use of population-based data and NHIRD records using a large sample size and having low loss to follow-up in the longitudinal design, including study and control cohorts. In addition, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single-buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. Therefore, the diagnoses of PKD based on ICD-9 codes in this study were highly reliable.

Some limitations of the current study should be clarified. First, data regarding some risk factors, such as tobacco smoking, alcohol consumption, and physical activity cannot be obtained from the NHIRD, as mentioned previously.[15] Second, biologic data, including echocardiographic parameters, and some crucial data on preexisting conditions such as thyroid dysfunction were also lacking. To overcome these limitations, associated factors such as COPD, coronary artery disease, and stroke were included in the multivariable Cox proportional hazard models. Third, although the diagnostic accuracy of the NHIRD has been validated in previous studies, 24-hour Holter monitoring is not routinely used for all AF diagnoses. Hence, asymptomatic AF is highly likely to have been underestimated in the study. Finally, data regarding the genetic analysis of PC1 and PC2 are lacking in the database, although this does not hinder the diagnosis of PKD.

In conclusion, AF is a common sustained arrhythmia in daily practice and often leads to multiple comorbidities and poor prognosis,[27] which eventually increase health care costs and mortality. Based on the findings of current study, we suggest that AF is associated with PKD patients. Notably, a remarkably high incidence rate and risk were observed in patients with PKD when multiple risk factors were combined. A high index of suspicion should be maintained when examining PKD patients with irregular betas. Early prophylactic therapy is warranted in these patients.

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