

## Causes and outcomes of hypereosinophilia in a tropical country

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### Abstract

**Background:** Hypereosinophilia (HE), defined by blood eosinophils  $> 1.5 \times 10^9/L$  persisting over one month, is commonly found in clinical practice.

**Objective:** This study aimed to explore etiologies, clinical characteristics, and outcome of HE.

**Methods:** The HE patients from a single center in Thailand during 2014-2019 were retrospectively reviewed.

**Results:** Among 166 HE patients, 102 (61.5%) cases had reactive HE ( $HE_R$ ) of which 52% was due to parasitic infections. Two-thirds of these patients were diagnosed based on the patients' response to empirical anti-parasite therapy. Without secondary causes, eosinophil-related symptoms were found in 20 (12.0%) patients (Hypereosinophilic syndrome: HES) of which three of them had myeloid neoplasms ( $HES_N$ ) and one case had lymphocytic variant HES (L-HES). Among 11 of 16 idiopathic HES ( $HES_I$ ) patients who were treated with systemic steroid, nine (81.8%) patients responded well, and two cases obtained symptom improvement with stable eosinophilia. There was 44 (26.5%) asymptomatic HE of undetermined significance ( $HE_{US}$ ) and 37 (84.1%) of them had HE for more than 6 months before diagnosis. Marked eosinophilia ( $> 10 \times 10^9/L$ ) was more common in HES (37.5%), but it was also found in  $HE_R$  (16.7%) and  $HE_{US}$  (11.4%). During the median follow-up period of 16 months, 82.9% (34/41) of  $HE_{US}$  cases remained asymptomatic while seven (17.1%) patients spontaneously recovered.

**Conclusion:** A therapeutic trial of anti-parasite is reasonable for asymptomatic HE in tropical countries. Most  $HES_I$  responded to systemic corticosteroids and  $HE_{US}$  showed benign courses without therapy.

**Key words:** Hypereosinophilia, Eosinophilia, Hypereosinophilic syndrome, Eosinophil disorders, Hypereosinophilia of undetermined significance

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### Introduction

Eosinophilia (Eosinophils  $> 0.5 \times 10^9/L$ ) is commonly detected in general clinical practice and usually caused by allergy or parasites. However, primary eosinophilic disorders are of concern.<sup>1,2</sup> According to the consensus criteria and classification by Valent P, et al.,<sup>3</sup> the term of hypereosinophilia (HE) was established and defined as having blood eosinophils  $> 1.5 \times 10^9/L$  twice and persistent for more than 1 month or presence of tissue HE with/without blood eosinophilia. Reactive HE ( $HE_R$ ) is diagnosed when the primary cause is identified.

If HE patients have eosinophil-mediated organ damage without any secondary cause, then the term of hypereosinophilic syndrome (HES) will be used. The classification of HE/HES was categorized according to its etiology. Neoplastic HES ( $HES_N$ ) is a clonal stem cell, myeloid or eosinophil neoplasm as per the World Health Organization's classification.<sup>4</sup> The lymphocytic variant HES (L-HES) is characterized by an increase of polyclonal eosinophils in response to cytokines secreted from clonal T-lymphocytes.<sup>5</sup> Idiopathic HES ( $HES_I$ ) is

used in symptomatic HE patients with no reactive or clonal diseases. Moreover, HE of undetermined significance ( $HE_{US}$ ) is defined by the absence of familial eosinophilia, reactive and neoplastic conditions causing HE, as well as no end-organ damage.<sup>3</sup>

In a previous 18-year retrospective study from National Institute of Health reported that there were 254 unexplained HE/HES adult patients and they were classified as follows: 47% had  $HES_p$ , 22% had  $HE/HES_R$ , 16% had L-HES, 11% had  $HES_N$  and 3% had  $HE_{US}$ .<sup>6</sup> In another single-center study conducted in Korea revealed that the predominant etiology of HE was malignancy, followed by allergy and skin diseases. However, this study enrolled only patients with eosinophils  $> 1.5 \times 10^9/L$ , regardless of duration.<sup>7</sup> The guideline for the investigation and management of HE was proposed.<sup>8,9</sup> However, these extensive investigations might not be applicable to countries with limited resources. Hence, this study explored the etiologies, clinical characteristics, management, and outcomes of HE in a tropical country.

## Materials and methods

This retrospective study enrolled patients with blood hypereosinophilia which is defined as having blood eosinophil  $> 1.5 \times 10^9/L$  at least two times for more than one month.<sup>3</sup> In addition, we also recruited HE patients who had blood eosinophil  $> 10 \times 10^9/L$  at least two times in less than one month because there is an urgent need to manage this disorder. All patients who were diagnosed with eosinophilia or HES by ICD10 at the King Chulalongkorn Memorial Hospital between 2014 and 2019 were enrolled into the study. All of their medical records and laboratory reports were thoroughly reviewed. The protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed consent was waived. The criteria and classification of eosinophilic disorders proposed by Valent P, et al., were used in this study.<sup>3</sup>

Parasitic infestations are common in Thailand. Anti-parasitic drugs, seven days of albendazole or two days of ivermectin, are usually prescribed to asymptomatic HE patients regardless of stool examination. The empirical anti-parasite responsive group was defined as resolution of HE after anti-parasitic treatment without evidence of parasite in the stool. Medical history, physical examination and basic laboratory investigations were reviewed to detect secondary causes of HE and eosinophil-related organ damages.

After secondary/reactive HE patients were excluded, further extensive HE/HES investigations such as bone marrow studies, karyotype, *FIP1L1-PDGFR*A mutation, T cell clonality, serum IgE, tryptase and vitamin B12 levels were requested, especially for symptomatic HES patients.

The statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL). The descriptive data were presented as percentages. The categorical data were analyzed using the Chi-square's tests or Fisher's exact test. A two-sided *P* value  $< 0.05$  was considered significant.

## Results

### Patients with eosinophilia

There were 657 patients with eosinophilia (eosinophil  $> 0.5 \times 10^9/L$ ) from 2014 to 2019. We excluded 378 patients with mild eosinophilia (eosinophil  $< 1.5 \times 10^9/L$ ) and 113 patients with transient moderate-to-severe eosinophilia (eosinophil  $> 1.5 \times 10^9/L$  for less than one month). One hundred and sixty-six HE patients were enrolled into the study.

Secondary causes of eosinophilia were identified in 102 (61.4%)  $HE_R$  cases. Eosinophil-mediated symptoms were detected in 20 (12.0%) patients and these patients were diagnosed with HES. These included 16 with  $HES_p$ , three with  $HES_N$ , and one with L-HES. Patients with  $HES_N$  had positive *FIP1L1-PDGFR*A myeloid neoplasm (1), systemic mastocytosis (1) and myeloproliferative neoplasm with eosinophilia (1). Forty-four (26.5%) HE patients without eosinophil-mediated organ damages and secondary causes were classified as  $HE_{US}$  (Figure 1).

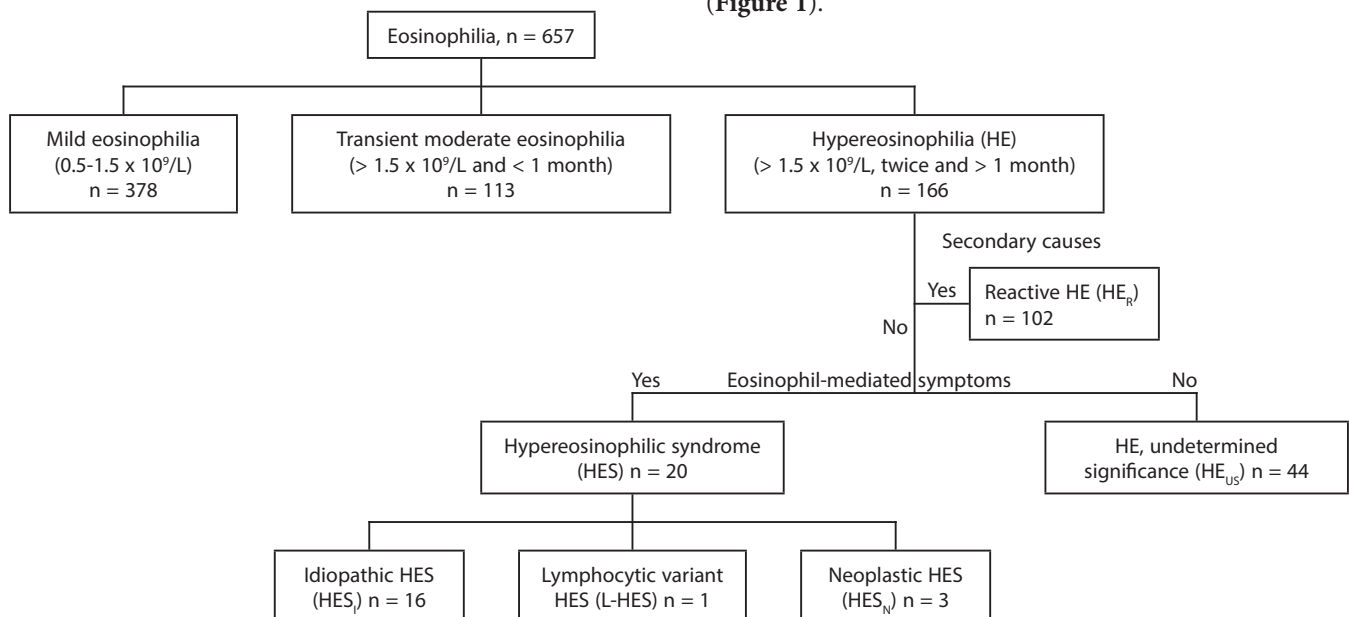


Figure 1. Study flow diagram of the eosinophilia patients.

### Reactive hypereosinophilia

Among 102 HE<sub>R</sub> patients, the causes of HE were parasitic infestations (52.0%), active malignancies (10.8%), autoimmune diseases (9.8%), non-parasitic infections (8.8%), allergic diseases (5.9%), drugs (2.9%), and hypoadrenalism (2%) (Figure 2A). Since Thailand is an endemic area for parasites, 35 of 53 infested patients were diagnosed to have parasites because of their response to empirical anti-parasitic treatments (66%). For patients with identifiable parasites, *Strongyloides stercoralis* (24.5%) was the most common parasite in asymptomatic patients from our cohort (Figure 2B). Other organisms, such as hook worm, gnathostoma, *Fasciola hepatica*, giardiasis, and *Entamoeba histolytica*, were less frequently detected. Eosinophilia resolved after anti-parasitic treatment in all these patients.

Among 11 malignancy cases, five of them were diagnosed with non-Hodgkin lymphoma and six had solid cancer. These included two patients with cervical cancer, two patients with cancer of unknown primary, one patient with oral cancer and one patient with bladder cancer. As for autoimmune diseases, four patients had vasculitis, three patients had Churg-Strauss syndrome, one patient had systemic lupus erythematosus, one patient had rheumatoid arthritis and one patient had autoimmune hyperthyroidism.

The severity of eosinophilia in HE<sub>R</sub> was usually mild or moderate. However, in our cohort showed that severe eosinophilia, defined by eosinophils over  $5 \times 10^9/L$ , could occur in all causes except for hypoadrenalism. In addition, marked eosinophilia ( $> 10 \times 10^9/L$ ) was detected in patients with active malignancies, parasitic infestations, non-parasitic infections, and autoimmune diseases (Figure 2C).

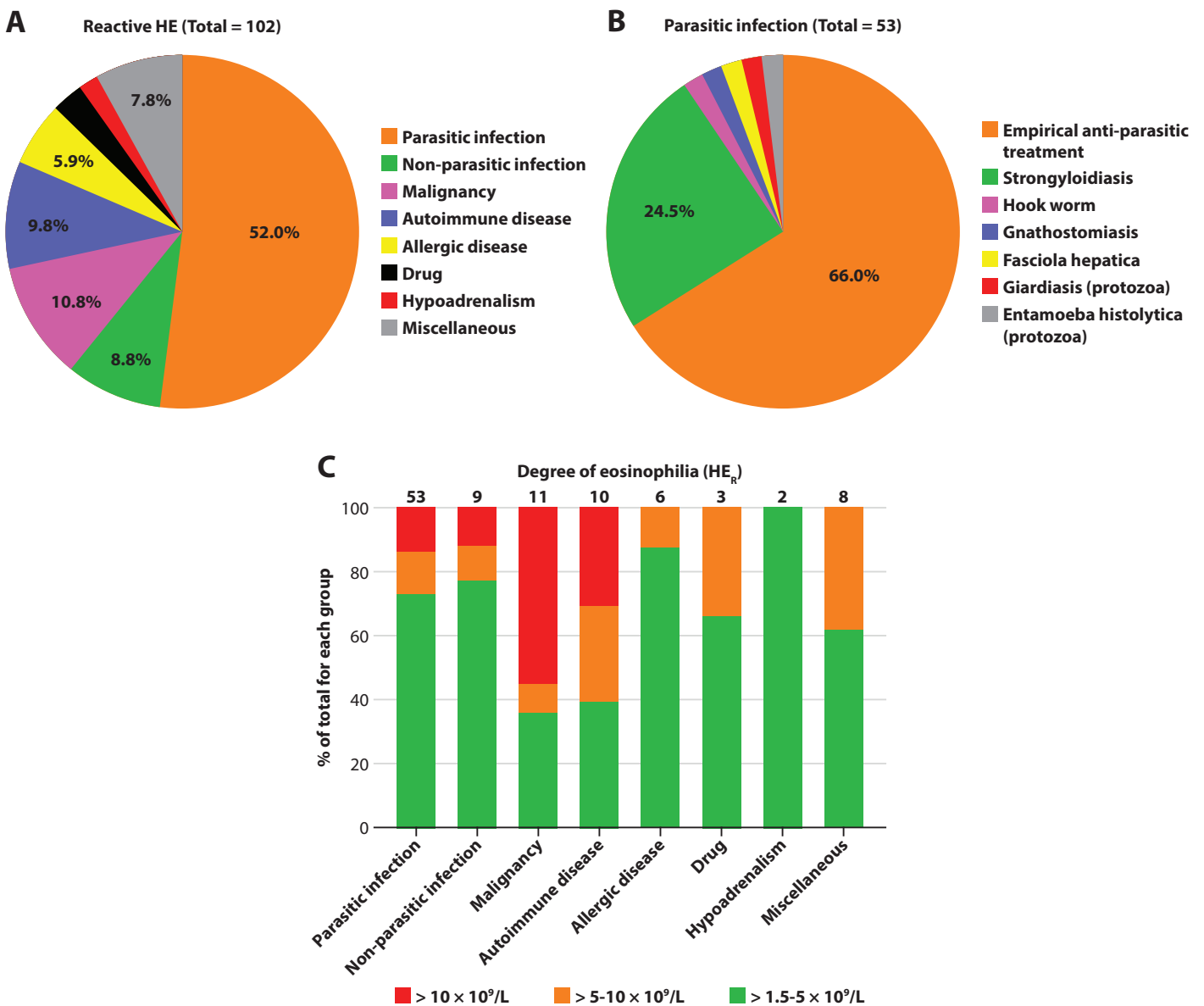


Figure 2. Reactive hypereosinophilia (HE<sub>R</sub>). (A) Etiology, (B) Type of parasitic infestation, and (C) Severity of HE<sub>R</sub>.

**Idiopathic hypereosinophilic syndrome (Table 1)**

HES<sub>I</sub> and HE<sub>US</sub> are subsets of HE of unknown etiology after all proper investigations have been carried out. The presence of eosinophil-mediated organ damage was required for HES diagnosis [3]. However, in this cohort, ten of sixteen HES<sub>I</sub> patients were identified target organ damage with eosinophil infiltration in tissue biopsy from skin (7), esophagus (1), colon (1), and ascites fluid (1). The rest of them were diagnosed by clinical clues such as arterial thrombosis without other causes of thrombophilia (3), cardiac involvement (1), hematologic involvement (1), and hepatitis with interstitial pulmonary infiltration (1). The median age of HES<sub>I</sub> patients was 54 (range 18-72) years. The male to female ratio of HES<sub>I</sub> was 2.6:1. Sixty three percent of HES<sub>I</sub> patients had severe eosinophilia (> 5 × 10<sup>9</sup>/L). Thirty eight percent of HES<sub>I</sub> patients had marked eosinophilia (> 10 × 10<sup>9</sup>/L). Twenty five percent of HES<sub>I</sub> patients presented with multiple organ involvement. The most common manifestation was skin lesions from eosinophilic infiltration without specific dermatological disorder. Gastrointestinal diseases, such as eosinophilic colitis, esophagitis, or ascites, were frequently presented in HES<sub>I</sub> in combination with other organ involvement. All three thromboembolism patients were at arterial side. Thrombocytopenia and hepatosplenomegaly were detected as hematological system involvements in this cohort.

Bone marrow morphology and karyotype were evaluated in almost all of the HES<sub>I</sub> patients (93.8%). All bone marrows showed increased levels of eosinophils. Sixty seven percent of the bone marrows were hypercellular. The karyotypes appeared normal in all of the patients. *FIP1L1-PDGFR*A mutation test was done in 62.5% of HES<sub>I</sub> patients and showed negative result. Forty four percent of the HES<sub>I</sub> patients were assessed and demonstrated negativity for T cell clonality. Serum IgE, tryptase and vitamin B12 levels were less commonly investigated (Table 1). For patients who had available data, the IgE levels were high in all four patients. Normal tryptase levels were detected in three patients. One of two patients had a high level of vitamin B12.

The first-line systemic steroid treatment was prescribed to 68.8% of HES<sub>I</sub> patients. Most of treated patients (82%) received prednisolone 1 mg/kg/day. Two (12.5%) HES<sub>I</sub> patients were treated with topical steroid. However, three HES<sub>I</sub> cases were lost to follow-up before treatment initiation. The HES symptoms and eosinophilia were resolved in 81.8% of HES<sub>I</sub> patients that were treated with systemic steroid. For the local treatment group, their symptoms resolved but HE persisted. The median follow-up time was 28 (range 2-75) months. There were no HE-related deaths in this study.

**Hyper eosinophilia of undetermined significance**

HE<sub>US</sub> was HE of unknown cause in the absence of eosinophil-related tissue injury [5]. The median age of HE<sub>US</sub> patients was 58 (range 24-85) years. The male to female ratio of HE<sub>US</sub> was 1:1. HE<sub>US</sub> patients presented with longer durations of eosinophilia compared with HES<sub>I</sub> (84.1% vs 25% more than 6 months, respectively, *p* < 0.001). The majority (65.9%) of HE<sub>US</sub> patients had moderate eosinophilia. In our cohort, HE<sub>US</sub> patients were investigated for bone marrow morphology and karyotype (45.5%), *FIP1L1-PDGFR*A mutation (31.8%),

**Table 1. Clinical characteristics of idiopathic hypereosinophilic syndrome (HES<sub>I</sub>) and hyper eosinophilia of undetermined significance (HE<sub>US</sub>)**

	HES <sub>I</sub> (n = 16) (%)	HE <sub>US</sub> (n = 44) (%)	P-value
Age (years)	54 (18-72)	58 (24-85)	
Sex (male: female)	1:1	2.6:1	0.127
Degree of eosinophilia			0.061
Moderate	6 (37.5)	29 (65.9)	
Severe (> 5-10 × 10 <sup>9</sup> /L)	4 (25)	10 (22.7)	
Marked (> 10 × 10 <sup>9</sup> /L)	6 (37.5)	5 (11.4)	
Hyper eosinophilia duration prior diagnosis			0.000
> 1-3 months	8 (50)	2 (4.5)	
> 3-6 months	4 (25)	5 (11.4)	
> 6 months	4 (25)	37 (84.1)	
Eosinophil-mediated organ damage		N/A	
Dermatological system	7 (43.8)		
Neurological system	1 (6.3)		
Thromboembolism	3 (18.8)		
Cardiovascular system	1 (6.3)		
Pulmonary system	2 (12.5)		
Gastrointestinal system	5 (31.3)		
Hematological system	2 (12.5)		
Multiple organ system	4 (25)		
Underlying diseases			
ESRD on regular HD	0	13 (29.5)	
Moderate/severe eosinophilia		8/5	
Remission of cancer	0	6 (13.6)	
Liver disease	0	3 (6.8)	
DM/HT/DLP/Atherosclerosis	0	12 (34.1)	
Investigations performed			
Bone marrow examination	15 (93.8)	20 (45.5)	0.001
<i>FIP1L1-PDGFR</i> A mutation	10 (62.5)	14 (31.8)	0.041
T cell clonality	7 (43.8)	14 (31.8)	0.541
Serum IgE level	4 (25)	5 (11.4)	0.230
Serum tryptase	3 (18.8)	7 (15.9)	1.0
Serum vitamin B12 level	2 (12.5)	5 (11.4)	1.0

Table 1. (Continued)

	HES <sub>I</sub> (n = 16) (%)	HE <sub>US</sub> (n = 44) (%)	P-value
Treatments			
Systemic steroid	11 (68.8)	2 (4.5)	
Local treatment	2 (12.5)	-	
Observation	-	41 (93.2)	
Loss to follow-up before therapy	3 (18.7)	1 (2.3)	
Treatment responses			
Improved HE/HES after steroid	9/11 (81.8)	2/2 (100)	
Stable HES after steroid	2/11 (18.2)	-	
Improved HE without steroid	-	7/41 (17.1)	
Stable HE/HES without steroid	2/2 (100)	34/41 (82.9)	

ESRD: end-stage renal disease; HD: hemodialysis; DM: diabetes mellitus; HT: hypertension; DLP: dyslipidemia.

and T cell clonality (31.8%) (Table 1). Serum IgE, tryptase and vitamin B12 levels were not frequently evaluated. For patients who had available data, all bone marrows showed that there were high levels of eosinophils. Forty percent of the bone marrows were hypercellular. All karyotypes appeared normal. The IgE levels were high in three of the five patients. Normal tryptase levels were detected in all seven patients. Three patients had high levels of vitamin B12.

Standard management of HE<sub>US</sub> was observation (93.2%). Among untreated HE<sub>US</sub> patients, 82.9% (34/41) of them remained asymptomatic with stable eosinophilia during the median follow-up time of 16 (range 3-107) months. Moreover, seven (17.1%) untreated HE<sub>US</sub> patients had spontaneous improvement of HE. Two asymptomatic HE<sub>US</sub> patients with extremely high eosinophil ( $10-30 \times 10^9/L$ ) received systemic steroid and their eosinophilia were resolved. No eosinophil-related symptom and/or extremely increase eosinophil levels was observed during the follow-up period. Interestingly, there were 13 (29.5%) HE<sub>US</sub> patients diagnosed with end-stage renal disease and were treated with regular hemodialysis.

## Discussion

Etiologies of HE/HES are different across various geographic regions. The present study from Thailand showed that the most common secondary cause was parasitic infestation. Notably, HES was diagnosed in 12% of HE patients in our cohort suggesting that symptomatic HE was not uncommon in Thailand. Therefore, in clinical practice, it is important to detect eosinophil-mediated organ damages, especially the skin, gastrointestinal tract and arterial thromboembolism. All necessary investigations, such as bone marrow morphology, karyotype, *FIP1L1-PDGFR*A mutation test and T cell clonality, should be done in all HES patients,<sup>4,5,10,11</sup> even though there are lower incidences of *FIP1L1-PDGFR*A-positive neoplasm

and L-HES in our cohort. Moreover, systemic steroid was an effective treatment in most HES<sub>I</sub> patients as the result of the 82% respond rate.

Aside from detecting eosinophil-related symptom, secondary causes of HE should be explored at the first visit to exclude HE<sub>R</sub>. Although, severe and marked eosinophilia frequently occurred in HES, these were present in 33.3% and 16.7% of HE<sub>R</sub> patients, respectively. For asymptomatic HE patients in tropical country, parasitic infestation remains a common problem in Thailand as well as other developing countries. Nuchprayoon S, et al. reported that the prevalence of parasitic infestations was 8.9% according to the routine stool examinations. The most identified parasite was *strongyloides stercoralis* (33.4%).<sup>12</sup> It is possible that a single stool examination may not be able to detect the parasites,<sup>13,14</sup> thus other therapeutic diagnosis may be used. In our center, we usually prescribed albendazole 400 mg twice daily for 7 days or ivermectin 200 mcg/kg once daily for 2 days. And eosinophil count was reevaluated after treatment for 3-4 weeks. In this cohort, 66% of the patients were diagnosed by HE resolution after an empirical anti-parasitic treatment. However, stool examination should also be investigated.

After HE<sub>R</sub> and HES patients were excluded, HE<sub>US</sub> was a presumptive diagnosis. In limited resource country, the symptom and severity of eosinophilia possibly biased physician judgement for more extensive investigations. Besides asymptomatic presentation, HE<sub>US</sub> manifested with significantly longer durations of eosinophilia prior to diagnoses (> 6 months) and trend to have less severe eosinophilia compared with HES<sub>I</sub>. In addition, 29.5% of HE<sub>US</sub> patients had underlying end-stage renal disease and had regular hemodialysis. This may be related to allergic reactions to hemodialysis circuits and, therefore, could not be definitely differentiated from HE<sub>R</sub>.<sup>15</sup>

The standard treatment of HE<sub>US</sub> is to closely monitor and observe the patient. Almost all HE<sub>US</sub> patients (93.2%) were followed without therapy and 82.9% of them remained stable. This was consistent with the findings from previous studies that HE<sub>US</sub> has a benign clinical course.<sup>16,17</sup> However, Pohlkamp C, et al. showed that myeloid gene mutations were detectable in 11.5% of HE<sub>US</sub> cases using next-generation sequencing.<sup>18</sup> In another study which monitored their patients yearly through extensive laboratory tests, there were early T-cell aberrancy among HE<sub>US</sub> patients.<sup>19</sup> Therefore, a longer clinical follow-up period is needed to draw a definitive conclusion.

The limitation of this study is that most of the HE<sub>US</sub> patients did not receive all of the laboratory investigations as described above due to the nature of a retrospective cohort and the limited-resource country. Recent study reported 80% of secondary HE/HES in Canadian cohort with extensive evaluation.<sup>20</sup> But there were only nine asymptomatic patients in the Canadian cohort. As for our cohort, there were 44 presumptive HE<sub>US</sub> patients of which 83% of them remained asymptomatic and had stable hypereosinophilia for up to 16 months. In order to diagnose patients with HE<sub>US</sub>, full investigations are necessary. However, close monitoring and prompt management of HE<sub>US</sub> patients are also important, especially in limited-resource country.



In summary, a therapeutic trial of anti-parasite should be considered for asymptomatic HE in tropical countries. Most HES<sub>I</sub> responded to systemic corticosteroids. Furthermore, untreated HES<sub>US</sub> had benign clinical courses and approximately one-sixth of them showed spontaneous recovery.

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## Disclosure of interest

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## Author contributions

- C.C. initiated the hypothesis, collected and analyzed the data, including writing the manuscript.
- N.U. gave advise.
- C.M. gave advise.
- P.R. gave advise and edited manuscript.

## References

1. Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. *Br J Haematol.* 2006;133:468-92.
2. Simon D, Simon HU. Eosinophilic disorders. *J Allergy Clin Immunol.* 2007;119(6):1291-300.
3. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol.* 2012;130:607-12.
4. Bain BJ, Horny HP, Arber DA, Tefferi A, Hasserjian RP. Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement. In: Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Update to 4th Edition. Lyon: World Health Organization; 2017. p. 71-9.
5. Roufosse F, Cogan E, Goldman M. Lymphocytic Variant Hypereosinophilic Syndromes. *Immunol Allergy Clin North Am.* 2007;27:389-413.
6. Williams KW, Ware J, Abiodun A, Holland-Thomas NC, Khoury P, Klion AD. Hypereosinophilia in Children and Adults: A Retrospective Comparison. *J Allergy Clin Immunol Pract.* 2016;4(5):941-7.
7. Kim DW, Shin MG, Yun HK, Kim SH, Shin JH, Suh SP, et al. Incidence and Causes of Hypereosinophilia in the Patients of a University Hospital. *Korean J Lab Med.* 2009;29(3):185-93.
8. Butt NM, Lambert J, Ali S, Beer PA, Cross NCP, Duncombe A, et al. Guideline for the investigation and management of eosinophilia. *Br J Haematol.* 2017;176:553-72.
9. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2019;94(10):1149-67.
10. Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU, et al. Approaches to the treatment of hypereosinophilic syndromes: A workshop summary report. *J Allergy Clin Immunol.* 2006;117:1292-302.
11. Schwaab J, Jawhar M, Naumann N, Schmitt-Graeff A, Fabarius A, Horny H-P, et al. Diagnostic challenges in the work up of hypereosinophilia: pitfalls in bone marrow core biopsy interpretation. *Ann Hematol.* 2016;95(4):557-62.
12. Nuchprayoon S, Siriyasatien P, Kraivichian K, Porksakorn C, Nuchprayoon I. Prevalence of parasitic infections among Thai patients at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand. *J Med Assoc Thai.* 2002;85 Suppl1:S415-23.
13. Branda JA, Lin TD, Rosenberg ES, Halpern EF, Ferraro MJ. A rational approach to the stool ova and parasite examination. *Clin Infect Dis.* 2006;42(7):972-8.
14. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. *Clin Infect Dis.* 2001;33(7):1040-7.
15. Hildebrand S, Corbett R, Duncan N, Ashby D. Increased prevalence of eosinophilia in a hemodialysis population: Longitudinal and case control studies. *Hemodial Int.* 2016;20(3):414-20.
16. Helbig G, Hus M, Francuz T, Dziaczkowska-Suszek J, Soja A, Kyrzcz-Krzemien S. Characteristics and clinical outcome of patients with hypereosinophilia of undetermined significance. *Med Oncol.* 2014;31(1):815.
17. Ang AL, Wong RX, Zhuang QY, Linn YC. Natural history of severe eosinophilia with uncertain aetiology and proposals on a practical approach to its management. *Intern Med J.* 2012;42(8):928-33.
18. Pohlkamp C, Vetro C, Dicker F, Meggendorfer M, Kern W, Haferlach C, et al. Evidence of clonality in cases of hypereosinophilia of undetermined significance. *Leuk Lymphoma.* 2019;60(8):2071-4.
19. Chen YY, Khoury P, Ware JM, Holland-Thomas NC, Stoddard JL, Gurprasad S, et al. Marked and persistent eosinophilia in the absence of clinical manifestations. *J Allergy Clin Immunol.* 2014;133(4):1195-202.
20. Moller D, Tan J, Gauran DTV, Medvedev N, Hudoba M, Carruthers MN, et al. Causes of hypereosinophilia in 100 consecutive patients. *Eur J Haematol.* 2020;105(3):292-301.