

# The Prevalence and Patient Characteristics of Primary Antibody Deficiencies in a Tertiary Care Setting in North Cyprus

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## BACKGROUND/AIMS

Primary antibody deficiencies (PADs) are the most common group of primary immunodeficiency disorders that present with a wide range of clinical features. We conducted this study to evaluate the frequency and characteristics of patients with PADs.

## MATERIAL and METHODS

The medical records of 160 children (M:F 99:61, mean age  $42.39 \pm 28.44$  months) were retrospectively reviewed from the Near East University Hospital database. Children who had PADs were then compared according to their demographic, clinical, and laboratory findings.

## RESULTS

A total of 97 children were diagnosed with PADs (49 THGI, 31 IgGD, 1 SlgAD, 8 CVID, 6 IgMD, and 2 PHGI)\*. Patients with THGI had the youngest age at the time of diagnosis ( $27 \pm 16.40$  months), and those with CVID had the oldest age at the time of diagnosis ( $81.62 \pm 49.9$  months old) compared with children in other PAD groups. In the HGG group, 63.9% of children presented with both recurrent wheezing/cough and infections, 22.7% had only recurrent infection, 13.4% of them had only recurrent wheezing/cough, and 71.7% of the children were atopic. At the end of the 2-year follow-up period, 8 patients (5 THGI and 3 IgGSD) out of 70 with HGG recovered.

## CONCLUSION

PADs generally present with recurrent infections and/or recurrent bronchoconstriction unresponsive to standard asthma treatment. Evaluation of the immune system is important to increase the quality of life of these patients and also decrease the healthcare costs.

**Keywords:** Allergy, hypogammaglobulinemia, immunoglobulin, recurrent infections

## INTRODUCTION

Primary immunodeficiency disorders (PID) are defined on the basis of the component of the body's immune system that is missing or not functioning properly (1). These disorders are caused due to hereditary genetic defects. Approximately 300 single gene disorders have been reported with underlying symptoms, including recurrent infections, allergy, autoimmunity, and malignancy (2). Hypogammaglobulinemia (HGG) is one of the major groups of PIDs that is caused due to various defects in the B-cell lineage or B-cell function resulting in low levels of immunoglobulins in the blood circulation. This affects the body's immune response and causes a broad spectrum of clinical features ranging from asymptomatic diseases to severe and recurrent infections, chronic inflammation, and autoimmunity (3). Major B-cell immunodeficiencies include transient hypogammaglobulinemia of infancy (THGI), IgM deficiency (IgMD), Bruton agammaglobulinemia, selective IgA deficiency (SlgAD), IgG subclass deficiency (IgGSD), and common variable immunodeficiency (CVID) (4).

The majority of patients can lead normal lives by taking prophylactic antibiotics. However, those with severe infections require intravenous immune serum globulin (IVIG) treatments (5).

\*Abbreviations: CVID, common variable immune deficiency; THGI, transient hypogammaglobulinemia of infancy; PHGI, protracted hypogammaglobulinemia of infancy; IgMD, IgM deficiency; SlgAD, selective IgA deficiency; IgGSD, IgG subclass deficiency.

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Epidemiological studies have reported geographical and racial variations in both the prevalence and pattern of immunodeficiencies (6). In adults, IgA deficiency is the most common disorder (I:400–800). Bruton (X-linked) agammaglobulinemia affects 1 in 10,000–200,000 males, whereas females do not manifest any clinical symptoms as they are only carriers (7). The incidence rate of CVID is 1:10,000–50,000 depending on particular race (I).

The national registry for incidence and prevalence rates of PID diseases is currently not available in North Cyprus. Early diagnosis of hypogammaglobulinemia is important to prevent fatal results and complications during the follow-up period of their current symptoms.

In the present study, we aimed at determining the rate of any humoral PID diseases among children who were admitted to our hospital, which is a tertiary care setting in North Cyprus.

## MATERIAL AND METHODS

### Ethical Approval

This study was approved by the Institutional Ethics Evaluation Board (2017/43-359) on January 18, 2017.

### Informed Consent

Informed consent was not necessary as this was a retrospective study.

### Study Population

This investigation was designed as a single-center retrospective study including those children who were under follow-up in the Division of Paediatric Allergy and Immunology in the tertiary hospital in Cyprus for a 3-year interval.

Children who had recurrent infection (8-10) and/or recurrent wheezing/cough and were unresponsive to standard asthma medications (II) were investigated for HGG.

Children who did not apply to the Division of Paediatric Allergy and Immunology and/or had secondary immunodeficiencies, e.g., HIV, were excluded based on a commercially available ELISA test combo reagent kit for detecting HIV Ag/Ab (Architect System, Abbott, Wiesbaden, Germany).

### Study Design

The demographic, clinical, and laboratory data of the children included in this study were collected from the hospital's database retrospectively.

### Main Points:

- The admission to the hospital of PAD patients were mainly, recurrent infections and/or recurrent bronchiolitis unresponsive to standard asthma treatment.
- THG had been found to be the major subgroup of PAD in which 10% of them recovered in a 2 year follow up period.
- Early diagnosis and the follow up period of PAD are important in order to increase the quality of life of the patients as well as to decrease the healthcare costs.

Details regarding gender, age, family history of immunodeficiency, allergy, recurrent infections, follow-up period, remission of hypogammaglobulinemia, initial and final treatments, serum Ig levels, IgG subgroup levels, lymphocyte subset percentages, specific antibody responses, skin prick test, or allergen-specific IgE results were recorded.

### Follow-up Period and Treatment

Patients who had fewer than six mild infections in a year were not given prophylactic treatment.

Patients who had more than six infections such as upper respiratory tract infections, otitis media, sinusitis, and gastroenteritis requiring antibiotic treatment were administered an oral prophylactic treatment with trimethoprim-sulfamethoxazole (Trim-Sulf).

Those who failed to respond to the oral antibiotic prophylaxis and those who required hospitalization two or more times a year due to severe infections such as pneumonia, bronchopneumonia, and cellulitis were administered IVIG at a dosage of 0.5 g/kg every 21 days.

For the treatment of asthma, inhaled corticosteroids (ICSs) were used as a first-line medication. The dosage of ICSs was adjusted according to the severity of symptoms based on GINA guideline recommendations (II). The patients were examined every 2 months to adjust the ICS dosage.

The immune system was evaluated by measuring the serum Ig and IgG subclass levels. Further tests such as determination of the lymphocyte subset percentages and the specific antibody responses were performed if indicated by the clinician.

### Laboratory Studies

#### Atopy

For the determination of the presence of atopy, skin prick tests were performed using 21 common aeroallergens, including *Dermatophagoides farinae*, *D. pteronyssinus*, *Alternaria*, *Aspergillus mix*, *Penicillium mix*, *Candida albicans*, Betulaceae, *Aesculus hippocastanum*, *Olea europaea*, *Plantago*, *Artemisia*, *Parietaria*, *Secale cereale*, *Triticum vulgaris*, *Acacia dealbata*, and a mixture of five grasses, feathers, cat hair, dog hair, and cockroach (Stallergenes, Antony, France). Histamine and saline were used as positive and negative controls, respectively. A drop of each allergen extract was placed on the volar surface of the left forearm and penetrated using a staller point. After 15 min, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. A wheal diameter of at least 3 mm greater than that in the negative control was considered as positive.

#### Immunological Tests

All the equipment used for laboratory analyses are calibrated routinely in the laboratory of our hospital. Furthermore, negative and positive control samples were used before analyzing the patient's serum samples.

#### Assessment of Immunoglobulin Levels

Peripheral venous blood samples of the patients were centrifuged at 2000×g for 10 min to obtain serum.

Serum IgG, IgA, and IgM levels were measured by the turbidimetric method using Roche Cobas c3II and commercially available kits (Roche Diagnostics, Mannheim, Germany).

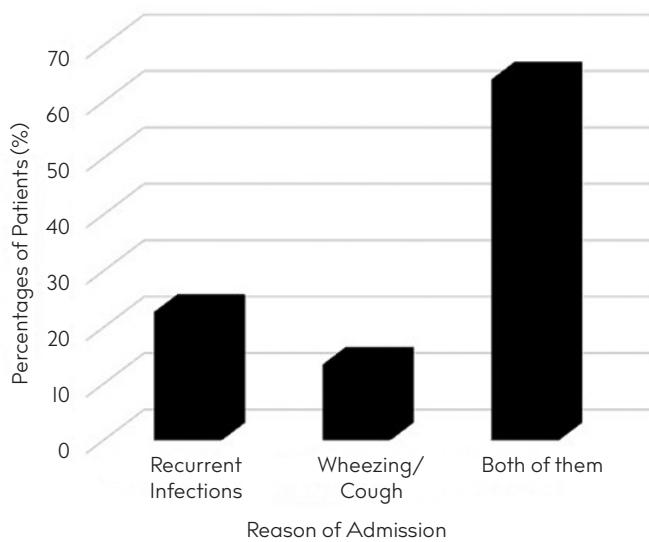
Serum IgE levels were measured by fully automated ELISA, Roche Cobas e4II using commercially available kits (Roche Diagnostics, Mannheim, Germany).

Serum IgG subclasses (IgG1, IgG2, and IgG3) were evaluated by nephelometry using commercially available kits.

All Ig results were evaluated according to the normal $\pm$ 2SD values based on the levels of healthy Turkish children according to age (I2). Values lower than 2SD were accepted as low.

### Lymphocyte Subset Analysis

Lymphocyte subpopulation analysis was performed by flow cytometry (BD FACS Calibur, BD Biosciences, San Jose, CA, USA). Lymphocyte subsets derived from peripheral blood were counted by fluorescence-activated cell sorting (FACS), including total lymphocytes (CD45+), total T cells (CD3), helper T cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8+), B cells (CD19+), NK cells (CD16/56+), and active T cells (CD3/anti-HLA DR). The results were evaluated according to the normal $\pm$ 2SD values based on the age of Turkish children (I3). Values lower than 2SD were accepted as low.



**FIGURE I.** Number of patients with HGG according to the reason of admission  
HGG: hypogammaglobulinemia

### Antigen-specific Antibody Response

Antigen-specific antibody responses were evaluated by anti-tetanus toxoid IgG antibody level Euroimmuno IgG ELISA (catalog no: EI 2060-9601 G) Pneumococcus IgG, ELIZEN/ ZenTech (catalog no: E-DG-96), and anti-Hbs, fully automated ELISA Roche Cobas e4II (catalog no: EI 2060-9601 G) using commercially available kits (Roche Diagnostics, Mannheim, Germany).

### Statistical Analysis

Statistical analyses were performed using the IBM SPSS software package for Windows (release 20.0.0, SPSS Inc, Chicago, IL, USA). In the descriptive statistics, prevalence rates were expressed as mean (SD) and percentages. Chi-square, Kruskal-Wallis, and Mann-Whitney U tests were used for analyses. P values <0.05 were considered to be statistically significant.

## RESULTS

A total of 160 children, including 61 (38.1%) females and 99 (61.9%) males, who met the inclusion criteria were enrolled in this study. Of these children, 35 (21.9%) were admitted with recurrent infections, 25 (16.6%) had with recurrent cough/wheezing, and 100 (62.5%) children had both recurrent infections and recurrent cough/wheezing. After further laboratory investigations, 97 (60.6%) children were diagnosed with humoral PID and defined as the hypogammaglobulinemia (HGG) group (mean $\pm$ SD age: 43.07 $\pm$ 30.67 months, male/female: 66/31). The number, gender, and mean age of these patients were presented according to the type of PID that they had at the time of diagnosis. The most frequently diagnosed immune deficiency diseases among the children with HGG were THGI 49 (50.5%) and IgG subclass deficiency 31 (32%). The mean age at the time of diagnosis was 27 months for patients with THGI, 57.35 months for those with IgGSD, 49 months for those with S IgAD, 81.62 months for children with CVID, 40.50 months for those with IgMD, and 66 months for children with protracted hypogammaglobulinemia (PHGI) (Table I).

In the HGG group, the majority of children (63.9%) had both recurrent wheezing/cough and infections, 22.7% of them had only recurrent infection, and 13.4% of the children presented with only recurrent wheezing/cough that was unresponsive to standard asthma treatment (Figure I).

Among the 49 children who were diagnosed with THGI, 29 were admitted to the hospital with both recurrent cough/wheezing and recurrent infections, of whom 14 had only recurrent infections and 6 had recurrent wheezing/cough.

Among the majority of children who were diagnosed with IgG subgroup deficiency, 20 (64.5%) had recurrent infection together-

**TABLE I.** Patients' demographic data according to their PADs

	THGI	IgGSD	S IgAD	CVID	IgMD	PHGI
Number						
n (%)	49 (50.5)	31 (32)	1 (1)	8 (8.2)	6 (7.9)	2 (2.1)
Gender (Male/Female)	37/12	16/15	1/0	5/3	5/1	2/0
Age at the time of Diagnosis (months $\pm$ SD)	27.00 $\pm$ 16.40	57.35 $\pm$ 29.05	49.00 $\pm$ 0.00	81.62 $\pm$ 49.96	40.50 $\pm$ 18.45	66.00 $\pm$ 7.07

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; S IgAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

er with wheezing/cough, 6 (19.3%) had only recurrent infection, and 5 had only wheezing/cough.

Patients who were admitted to the Division with complaints of only asthmatic symptoms belonged to the THGI, Ig subgroup deficiency, PHGI and IgM deficiency groups, 6 (12.2%), 5 (16.1%), 1 (100%), and 1 (100%) in numbers respectively (Table 2).

**TABLE 2.** Reasons of admission among patients with PAD

PADs (n=97)	Diagnosis at admission n (%)		
	Recurrent Infection	Recurrent wheezing/ cough	Both of them
THGI (n=49)	14 (28.6%)	6 (12.2%)	29 (59.1%)
IgGSD (n=31)	6 (19.4%)	5 (16.1%)	20 (64.5%)
SIGAD (n=1)	0 (0.0%)	0 (0.0%)	1 (100%)
CVID (n=8)	1 (100%)	0 (0.0%)	7 (87.5%)
IgMD (n=6)	0 (0.0%)	1 (100%)	5 (83.3%)
PHGI (n=2)	1 (100%)	1 (100%)	0 (0.0%)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIGAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

**TABLE 3.** Family history of allergic diseases, PADs, and consanguineous marriage for patients with PAD

PADs (n=97)	Family History		
	Allergic Diseases	PAD	Consanguineous Marriage
THGI (n=48)	18 (37.5)	1 (2.0)	2 (4.2)
IgGSD (n=30)	19 (63.3)	2 (6.7)	0 (0.0)
SIGAD (n=1)	0 (0.0)	0 (0.0)	0 (0.0)
CVID (n=7)	4 (57.14)	1 (14.3)	0 (0)
IgMD (n=6)	3 (50)	2 (33.3)	1 (16.7)
PHGI (n=1)	0 (0.0)	0 (0.0)	0 (0.0)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIGAD: selective IgA deficiency; IgGSD: IgG subclass deficiency.

**TABLE 4.** Medications that were given to patients with PAD

Diagnosis (n)	Trim-sulf n (%)	IVIG n (%)	Trim-sulf + IVIG n (%)	No. of patients requiring treatment n (%)
THGI (n=49)	16 (32.7)	1 (2)	-	17 (17)
CVID (n=8)	6 (75)	1 (12.5)	-	7 (87.5)
IgGSD (n=31)	9 (29)	-	-	9 (29)
IgMD (n=6)	-	-	1 (16.7)	1 (16.7)

PAD: primary antibody deficiency; CVID: common variable immune deficiency; THGI: transient hypogammaglobulinemia of infancy; PHGI: protracted hypogammaglobulinemia of infancy; IgMD: IgM deficiency; SIGAD: selective IgA deficiency; IgGSD: IgG subclass deficiency; Trim-Sulf: Trimethoprim/sulfamethoxazole; IVIG: Intravenous immunoglobulin.

Among the HGG group, 71.7% of patients were sensitive to at least one allergen. Atopy was present in 53.1% of children in the non-HGG group (Figure 2).

The highest rate of atopy was observed in patients with Ig subgroup deficiency [17/23 (73.9%)], followed by patients with THGI [17/25 (68%)].

Among the group with primary antibody deficiencies (PADs; 97 patients), 60 patients were evaluated for atopy, and it was detected in 43/60 (71.7%) children with PADs. Among these patients, 17/25 (68%) had THGI, 17/23 (73.9%) had IgGSD, 5 (83.3%) had CVID, and 2 (50%) had IgMD.

Children in the HGG group were further evaluated based on the family history of allergic diseases, PADs, and consanguineous marriage of parents, whose prevalence rates were found to be 48.4%, 6.4%, and 3.2%, respectively.

Children who were diagnosed with IgMD had the highest prevalence of positive family history for both allergic diseases (50%) and PADs (33.3%) and also for the presence of consanguineous marriage among their parents (16.7%) (Table 3).

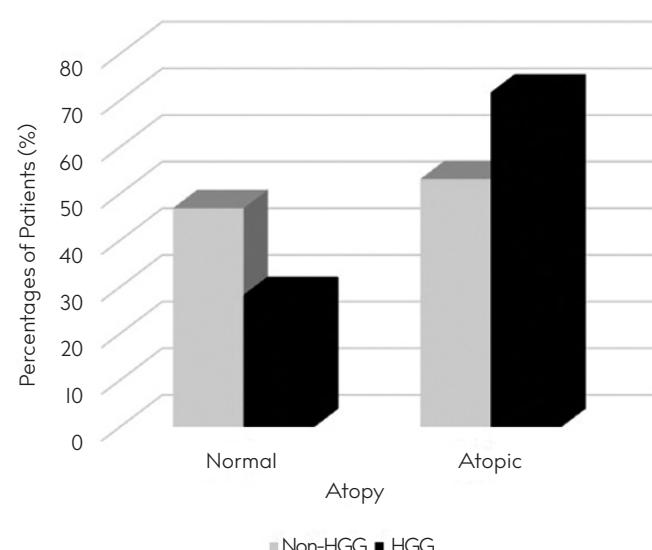
#### Treatment Follow-up

Patients with HGG were followed up for 2–48 months, with a mean follow-up period of 13 months.

Among patients with HGG, 3 (3.1%) were under IVIG treatment, 31 (32%) were under Trim-Sulf prophylaxis, and 25 (26.9%) were followed up without any medication.

Medications that were administered to the patients are summarized in (Table 4).

A total of 70 patients who had hypogammaglobulinemia were followed up for 2 years. During this period, eight patients had recovered, including five in the THGI group and three in the IgG3 subgroup deficiency group, indicating recovery rates of 4/40 (12.5%) and 3/17 (17.6%), respectively, during the 2-year follow-up.



**FIGURE 2.** Presence of atopy in the non-HGG and HGG groups  
HGG: hypogammaglobulinemia

## DISCUSSION

Among the 160 children evaluated for PADs who had presented with recurrent infections and/or recurrent wheezing/cough, 97 (60.6%) were identified as having HGG.

THGI was the most frequently diagnosed group of HGG that affected approximately half of our study population. This result was in accordance with a study performed in Turkey (6) reporting THGI as the most frequently detected PAD with a prevalence rate of 7/100,000. On the other hand, studies from Europe, Australia, and Japan reported SlgAD as the most common type of PAD (3, 14-16). In addition, CVID was reported as the most frequently diagnosed PAD in Ireland, Norway, and Egypt (17-19).

Especially in CVID cases, high prevalence of consanguineous marriage and autosomal recessive trait were claimed to be the reason for the high prevalence (3). In a study reported from Turkey, the rate of consanguineous marriage among the parents of children with PAD was found to be 9.7% (8), which was higher than that in our study population (3%).

In our study, males (61.9%) were more affected with PADs than females (38.1%), which was consistent with studies from Turkey, Europe, Iran, Kuwait, Israel, and Australia (8, 20-24).

IgG subgroup deficiency was the second most common type of PAD in our study population. The majority of cases belonged to the IgG3 deficiency group (96.77%), and one patient belonged to the IgG2 deficiency group (3.2%). In a previous study, the prevalence of IgG subgroup deficiency was reported to be 4.6/100,000, making it the third most common type of antibody deficiency (8). Karaca et al. (25) reported that IgG3 deficiency was the most common IgG subgroup deficiency with a prevalence rate of 77%, whereas isolated IgG2 deficiency was detected in 9% of the patients. In another study, IgG2 deficiency was reported as the leading IgG subgroup deficiency (25).

In our study, patients with THGI had the youngest age at the time of diagnosis ( $27 \pm 16.40$  months), and those with CVID had the oldest age at the time of diagnosis ( $81.62 \pm 49.9$  months old) compared with children in other PAD groups. These results were consistent with those of previous studies, e.g., 16.8 months for THGI cases and 60 months for CVID cases at the time of diagnosis (26) and  $45.12 \pm 31.08$  months for THGI cases and  $87.96 \pm 58.44$  months for CVID cases (27). In general, the majority of patients with CVID are diagnosed in late adolescence (28), which may be one of the reasons for the lower prevalence in our study.

In our study, recurrent infection was the most common presenting clinical feature in children with PADs (86.6%), which was consistent with the studies done in Turkey (58%) (6), Iran (89.6%) (3), Taiwan (54.5%) (29), and USA (87%) (30).

Among patients with PADs, 13 (13.4%) were admitted to the Division with only recurrent bronchoconstriction and wheezing. Among the PAD group of patients, six (4.6%) had THGI, five (3.8%) had IgG subgroup deficiency, 1 (7.7%) had PHGI, and 1 (7.7%) had IgM deficiency who presented with only asthmatic symptoms. In different studies, 5.4% (3) and 36.4% (26) of patients with PAD were reported to have asthmatic symptoms. In

addition, 7%-8% of children with slgMD were reported to have allergic diseases and asthma (31). In our study, despite the high atopy rates among patients with IgMD (50%), 16.6% of them had allergic asthma. Karaca et al. (25) reported 15% of atopy in Turkish children with IgG subgroup deficiency, and Chong et al. (25) reported 40% of allergic cases. In our study, 23 of the 31 patients were evaluated for atopy, and 17 (73.9%) were found to be atopic. Atopy was much more common in our patients with PAD compared to that in other studies.

In addition to infections, it has been reported that allergic symptoms occur as the first clinical manifestations of PADs (4.2%) (3), as also found in our study. The tendency to develop allergy among patients with SlgAD (22.2%) has been reported to be higher than that of other types of PADs (32, 33). However, in our study, children with IgGSD (73.9%), followed by those with THGI (68%), had higher rates of atopy. A dysregulation in the immune response contributing to defective antigen elimination in early childhood has been postulated to be a critical risk factor for the development of allergy (31).

The treatment given to these patients depends on the severity and frequency of symptoms. Mild cases with PAD can be observed without any treatment. Ig replacement is one of the important treatments in PAD. Three (8.8%) patients had received IVIG therapy.

Regarding the study limitations, larger number of patients could be included and the follow-up period could be extended to decide the number and type of certain PADs more clearly. Another limitation was that some of the patients had stopped coming for follow-up to our hospital according to their own will, so that we could not analyze any data obtained during the follow-up period, which reduced the amount of obtained information about the patients after the long-term follow-up.

In conclusion, early diagnosis and treatment of PAD are important for decreasing the morbidity and increasing the quality of life of those patients. Appropriate and early treatment would also decrease the healthcare costs. PADs have the highest prevalence among PIDs in several countries. In our study, the THGI and IgG subgroup deficiencies were the most common antibody deficiencies that may present not only with recurrent infections but also with recurrent bronchoconstriction unresponsive to standard asthma treatment. Evaluation of the immune system should be considered in children presenting with these types of clinical symptoms.

Creating a successful registry of PADs in North Cyprus would provide authorities adequate information for developing strategies for both diagnosis and treatment of patients with PADs.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Near East University Scientific Research Ethics Evaluation Board (Approval Date: 18.01.2017, Approval Number: YDU/2017/43-359).

**Informed Consent:** Informed consent is not necessary due to the retrospective nature of this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - N.B, B.S; Design - B.S, O.Y; Supervision - N.B; Resource - B.S, O.Y; Materials - N.B; Data Collection and/or Processing - B.S, O.Y; Analysis and/or Interpretation - B.S, O.Y; Literature Search - B.S, O.Y; Writing - B.S, O.Y; Critical Reviews - N.B.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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