CHARACTERISTICS OF INTRAVENOUS IMMUNOGLOBULIN DEMAND IN ADULT AND PAEDIATRIC PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By

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DISCLAIMER

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Master of Medicine in Transfusion Medicine. It is not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as a reference.

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In the name of Allah, the Most Beneficent, the Most Merciful. All praises be to Allah, Lord of the Worlds. Prayers and blessings be upon Prophet Muhammad, peace be upon him.

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MANUSCRIPT TABLES

LIST OF ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma, and Immunology
B-ALL	B-cell acute lymphoblastic leukaemia
CMV	Cytomegalovirus
CIDP	Chronic inflammatory demyelinating polyneuropathy
EMA	European Medicines Agency
ET	Exchange transfusion
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GVHD	Graft versus host disease
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
HSCT	Haematopoietic stem cell transplantation
HUSM	Hospital Universiti Sains Malaysia
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
ISG	Immune serum globulin
ITP	Immune thrombocytopenia
IVIG	Intravenous immunoglobulin
MMN	Multifocal motor neuropathy

NBC	National Blood Centre
PDMP	Plasma-derived medicinal products
PID	Primary immunodeficiency disease
RM	Ringgit Malaysia
UK	United Kingdom
UKM	Universiti Kebangsaan Malaysia
USM	Universiti Sains Malaysia
WHO	World Health Organization

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ABSTRAK

Pengenalan: Imunoglobulin intravena (IVIG) merupakan produk perubatan yang dihasilkan daripada plasma dan telah digunakan untuk merawat penyakit imun serta bukan imun. Kajian ini memfokuskan pada ciri-ciri dan indikasi penggunaan IVIG dalam kalangan pesakit di Hospital Universiti Sains Malaysia (USM).

Kaedah: Kajian keratan rentas retrospektif telah dijalankan bagi 218 pesakit yang dipreskripsi IVIG di Hospital USM. Data diekstrak daripada senarai permintaan IVIG yang direkodkan di Jabatan Farmasi dan nota-nota kes pesakit. Untuk analisis statistik, *Chi-square* dan *T-test* telah digunakan dan nilai p kurang daripada 0.05 dianggap signifikan.

Keputusan: Sebanyak 218 pesakit telah dipreskripsi IVIG di Hospital USM dari Januari 2019 hingga Disember 2020 yang mana 111 (50.9%) merupakan pesakit lelaki manakala 107 (49.1%) merupakan perempuan. Umur median pesakit ialah 7 tahun (julat 0.0–72.0). Indikasi yang paling kerap bagi indikasi berlabel IVIG ialah *immune thrombocytopenia* sebanyak 15 (32.6%) pesakit, manakala IVIG digunakan dengan paling kerap secara luar label bagi *neonatal jaundice* sebanyak 52 (30.2%) pesakit. Dalam kohort dewasa, IVIG paling kerap diberikan untuk *myasthemia gravis* sebanyak 26 (42.6%) pesakit, manakala kohort pediatrik menerima IVIG paling kerap untuk *neonatal jaundice* sebanyak 52 (46.8%) pesakit. Terdapat perbezaan yang ketara antara penggunaan IVIG secara berlabel dengan luar label ($p = 0.039$) dan kekerapannya ($p < 0.001$) dalam kedua-dua populasi dewasa dan kanak-kanak. Bangsa pesakit ($p = 0.011$) dan kategori klinikal dalam kalangan dewasa ($p = 0.002$) berkaitan secara signifikan dengan status indikasi penggunaan IVIG.

Kesimpulan: Terdapat perbezaan yang ketara antara penggunaan IVIG secara berlabel dan luar label dalam kalangan pesakit-pesakit Hospital USM. Garis panduan setempat mengenai penggunaan IVIG perlu dibangunkan bagi membantu para doktor dalam memberikan preskripsi IVIG dengan wajar kepada pesakit-pesakit.

Kata kunci: immunoglobulin intravena, indikasi luar label, indikasi berlabel, neonatal jaundice, immune thrombocytopenia

ABSTRACT

Introduction: Intravenous immunoglobulin (IVIG) is a plasma-derived medicinal product (PDMP) used to treat various immune and non-immunological diseases. This study focused on the characteristics and indications for IVIG demand among patients in Hospital Universiti Sains Malaysia (USM).

Methods: A retrospective cross-sectional study was conducted on 218 patients who were prescribed IVIG in Hospital USM. The data were obtained from the list of requests for IVIG recorded in the Pharmacy Department and the patient's case notes. For statistical analysis, Chi-squared and T-test analyses were performed, and a p-value of less than 0.05 was deemed significant.

Results: 218 patients were prescribed IVIG in Hospital USM from January 2019 until December 2020, of which 111 (50.9%) were males and 107 (49.1%) were females. The median age was 7 years old (IQR 0.00–45.25). The most common labelled IVIG indication was immune thrombocytopenia in 15 (32.6%) patients, whereas IVIG was given commonly as off-label in neonatal jaundice in 52 (30.2%) patients. In the adult cohort, IVIG was commonly given for myasthenia gravis, 26 (42.6%) patients, while the paediatric cohort received IVIG commonly for neonatal jaundice, 52 (46.8%) patients. There were significant differences between labelled and off-label IVIG usage ($p = 0.039$) and its frequency ($p < 0.001$) in both populations; adult and paediatric. Race ($p = 0.011$) and clinical category in adults ($p = 0.002$) had significant correlations with the status of IVIG usage.

Conclusion: There were significant differences between labelled and off-label usage of IVIG among all Hospital USM patients. A local guideline for IVIG usage should be developed to help clinicians in giving appropriate IVIG prescriptions.

Keywords: intravenous immunoglobulin, off-label indication, labelled indications, neonatal jaundice, immune thrombocytopenia

CHAPTER ONE:

INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter outlines the study on intravenous immunoglobulin (IVIG) demand among adult and paediatric patients in Hospital Universiti Sains Malaysia (USM). This chapter also highlights the research justifications and research questions.

1.2 Background of study

A wide range of therapeutic medicinal products derived from human blood plasma have been utilised for the prophylaxis and treatment of various immunological diseases (1). IVIG is a plasma product manufactured by isolating gamma-globulin fraction from the pooled plasma of 3,000 to 60,000 plasma donors that have been screened for transmissible diseases (2). The plasma undergoes alcohol fractionation with anti-aggregation and stabilisation processes that yield a product with 95% to 99% of highly purified polyvalent immunoglobulin G (IgG) with traces of immunoglobulin M (IgM), immunoglobulin E (IgE), immunoglobulin D (IgD), and immunoglobulin A (IgA) (2).

The complex mechanisms of actions of IVIG include anti-infective, immunomodulatory, and anti-inflammatory effects (2). In primary and secondary immunodeficiency diseases, IVIG contains antigen-specific IgG, which is important in providing ‘replacement’ antibodies by raising antibody levels and potentially boosting other immune functions, for instance, the removal of immunosuppressive complexes, thereby restoring normal immune function (2,3).

A number of mechanisms have been proposed to explain immunomodulatory effects of IVIG in autoimmune diseases. IVIG provides anti-idiotypes that neutralise

pathological IgG autoantibodies and alter the response of B-cells, modulating the immune response (2). Short-term actions include the blockade of Fc receptor-mediated events, cytokines regulation, and autoantibodies or superantigens neutralisation. In the long term, IVIG may promote downregulation of the production of antibodies and regulate the cytokines production by helper T-cells (3). There are several mechanisms that could potentially account for the anti-inflammatory effects of IVIG. These mechanisms include reducing complement-mediated damage, neutralising microbial toxins, and inhibiting leukocyte activation (3).

In the early 1940s, Cohn developed a process called cold ethanol precipitation with his co-workers to produce the first human IgG which was known as immune serum globulin (ISG) on a large scale (4). It was formulated at 165 mg/ml protein concentration that contained 0.1 g/l merthiolate, 0.3 molar glycine, and 0.9% sodium chloride with its pH adjusted to 6.8 ± 0.4. The solutions were stored at 5 degrees Celsius. The first immunoglobulins that were made available were only permitted to be administered subcutaneously or intramuscularly due to adverse reactions believed to have resulted from aggregates that were present during storage (5).

In 1952, Bruton successfully treated an 8-year-old patient with agammaglobulinaemia who suffered recurrent pneumococcal infections with subcutaneous immunoglobulin as replacement therapy (6). IVIG has since evolved into an important therapeutic product for treating patients with primary and secondary immunodeficiencies, and haematopoietic stem cell transplants. Other than that, chronic inflammatory demyelinating polyneuropathy (CIDP) and immune thrombocytopenia (ITP) are examples of disorders for which IVIG has a wide range of uses as an immunomodulatory agent (7). It has been designated as one of the important medicines

in the Model List of Essential Medicines by the World Health Organization (WHO) (8). Furthermore, several investigational uses of IVIG, such as those for Alzheimer's disease and COVID-19, were being researched (9,10).

The demand for IVIG is the most substantial driver of the plasma fractionation industry, and the immunoglobulin usage has increased annually by 6% to 8% (7,11). However, only 56 of the 171 reporting countries, as reported by WHO, produce plasma-derived medicinal products (PDMPs) obtained from the plasma fractionation, whereas the remaining 91 countries import all their PDMPs (12). Only 18% of plasma source originated from the Asia-Pacific region, with the United States serving as a major provider, accounting for 67% of the total plasma volume collected globally before the COVID-19 pandemic (7,13). Due to the decrease in red cell demand, the volume of recovered plasma collected in recent years has also declined, particularly during the COVID-19 pandemic. This situation occurred notably after the implementation of the patient blood management programme, fear of exposure to the SARS-CoV-2 infection, and other logistic factors (7,13,14).

Malaysia embarked on contract fractionation for plasma products in 1990 to obtain PDMPs that include IVIG (15). The country's National Blood Centre (NBC) in Kuala Lumpur is responsible for the plasma collections and exports 80,000 bags of plasma each year to Australia to obtain PDMPs such as factor VIII and factor IX concentrates, prothrombin complex concentrates, human albumin, and IVIG (15,16). Nevertheless, Malaysia is unable to develop its plasma fractionation plant due to the small number of plasma collections and limitations in terms of expertise (15).

Hospital Universiti Sains Malaysia (USM) obtains its supply of IVIG and other PDMPs through contract purchase. Until now, data for Hospital USM patients who have

been prescribed IVIG are still lacking. The issue is exacerbated by the lack of a local registry and usage guidelines for IVIG. Hence, the number and indications of actual IVIG usage for patients in the hospital remain unknown, and thus, this study is necessitated.

1.3 Literature review

Immunoglobulin has become more recognised as an important therapy to treat various types of medical conditions due to its properties as replacement therapy, immunomodulatory, and anti-inflammatory (17). It is manufactured from a large pool of purified plasma donated by thousands of donors that yields a product containing polyclonal immunoglobulins with more than 95% IgG (18).

Since the year 1990, IVIG in Malaysia has been obtained externally through contract fractionation of source and recovered plasma donated by thousands of blood donors to produce PDMPs (15). The NBC is responsible for more than three-fourths of IVIG supply in Malaysia. Each vial is supplied at an actual cost of RM500, but is subsidised at RM200 (19).

Food and Drug Administration (FDA) of the United States of America has licensed the use of IVIG for these clinical indications: i. primary immunodeficiency diseases; ii. prevention of bacterial infections in hypogammaglobulinaemic patients and recurrent bacterial infection due to B-cell chronic lymphocytic leukaemia (CLL); iii. reduction of serious bacterial infection in children with HIV infection; iv. prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation; v. prevention of coronary artery aneurysms in Kawasaki disease; vi. prevention or bleeding control in idiopathic thrombocytopenic purpura by increasing

platelet count; and vii. treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) (17).

Despite these FDA-approved indications for IVIG usage, it was used widely to treat a myriad of diseases in medicine, especially in immunology and neurology, as off-label; which no manufacturer has applied with the FDA as indications for IVIG usage (20). Many studies were carried out in other countries to compare labelled versus off-labelled IVIG indications among their patients.

A prospective study done in the United States of America over a period of eight months and involving 251 patients revealed that 107 (43%) patients were given IVIG for labelled indications. In contrast, 130 (52%) patients received IVIG off-label. However, IVIG therapy was not defined for 14 (5%) patients (21). A study carried out in Saudi Arabia between 2003 and 2005, involving a total of 305 patients, revealed that 109 (35.7%) patients received intravenous immunoglobulin (IVIG) for category A (FDA-labelled) indications (22). Similarly, an observational study conducted in Israel, spanning eight years and involving 1,117 patients, indicated that 622 (56%) patients were administered IVIG according to off-label FDA indications (23).

The indications for IVIG usage exhibit variation across different countries. In Israel, the indications for IVIG utilisation are determined by a committee of representatives from the Ministry of Health. This committee convenes on an annual basis to evaluate and authorise new pharmaceutical products and technologies for inclusion in the Israeli National List of Health Services, commonly referred to as 'The Health Basket.' According to Israeli Health Basket, IVIG may also treat multiple myeloma, Guillain-Barré syndrome (GBS), and as prophylaxis for hepatitis A in addition to FDA-approved indications (23).

In Europe, a consensus recommendation was developed for the optimal use of IVIG under the European Medicines Agency's (EMA) regulation, for which IVIG may also be used to prevent recurrent infection in secondary immunodeficiency, GBS, and multiple myeloma. However, more studies were recommended to assess the suitability of immunoglobulin therapy for patients with secondary immunodeficiency (24). The United Kingdom Clinical Guidelines for Immunoglobulin Use assigned prioritisation for the use of IVIG for each of the indications based on evidence with colour-coding: red for the highest priority indications with the greatest clinical needs, followed by blue, and grey for emerging indications. In the UK, IVIG may also be used in cases of alloimmune thrombocytopenia, haemolytic disease of the newborn, GBS, paraprotein-associated demyelinating neuropathy, and Stevens-Johnson syndrome. Contrary to FDA-licensed indications, IVIG use is not suggested for sepsis, immunodeficiency secondary to HIV infection in paediatrics, and bone marrow transplantation (25).

In Malaysia, IVIG is prescribed for ITP in adult and paediatric patients, but it is also used off-label for GBS, measles, Stevens-Johnson syndrome, and juvenile rheumatoid arthritis (26,27). However, there was no mention of the use of IVIG to prevent bacterial infection in paediatric HIV patients in the local clinical practice guidelines (28). Most Malaysian hospitals do not have comprehensive guidelines or protocols for IVIG use; therefore it could be overused for indications weakly supported by the latest evidence (29). The prescription for IVIG therapy primarily follows the Ministry of Health Drug Formulary and local clinical practice guidelines for specific diseases. However, there is limited reference to the recommendations strength and evidence category for off-label use from regulatory bodies such as the FDA, EMA, and the American Academy of Allergy, Asthma, and Immunology (AAAAI) (19).

A study done by a university medical centre in Malaysia evaluating the utilisation of IVIG and the clinical outcome found 61 (53%) cases in 115 patients receiving IVIG were used for FDA-approved indications. In comparison, 54 (47%) cases were used for off-label indications (30). In contrast, another study done in a government hospital in Malaysia found only one-third of the patients, 26 (33.3%), were given IVIG in compliance with FDA-approved indications, while the remaining two-thirds, 52 (66.7%) patients were given IVIG not compliant with FDA indications (19). The study carried out in a teaching hospital in Iran revealed comparable results, with 24 patients (33.3%) demonstrating adherence to FDA guidelines for the usage of IVIG. The remaining two-thirds of the patients received IVIG off-label with support in 32 (44.4%) patients, off-label without support in 6 (8.4%) patients, and 10 (13.9%) patients received IVIG for COVID-19 (31).

The commonest indication for IVIG differs across studies. Two studies conducted in three government tertiary hospitals in Malaysia found IVIG was commonly used for primary immunodeficiency, hypogammaglobulinemia, and other deficiency states (29,32). In contrast, another study at a tertiary referral hospital reported IVIG was primarily prescribed for immune thrombocytopenia (19). ITP was also reported as the most common indication for IVIG usage in the United States, Saudi Arabia, and Israel (21–23). In Iran, IVIG therapy was commonly given for treating GBS and CIDP (31).

Given the gap and deficiency of Hospital USM data, this study aims to determine the characteristics of IVIG demands in paediatric and adult patients.

1.4 Research justification

The limitation of the IVIG is its great cost burden and limited supply since it is manufactured externally. Therefore, IVIG usage should be justified according to its labelled indications to prevent wastage and risk to the patient for its undesirable side effects. In Malaysia, IVIG utilisation is underreported, and there is no centralised registry available locally for patients who were prescribed IVIG therapy. Hence, the exact number and the cost burden for IVIG usage in Malaysia remain unknown. The main gap identified here is the limited availability of data for IVIG usage, especially in Hospital USM. Therefore, a study of the characteristics of IVIG demand needs to be carried out in Hospital USM. This study aimed to characterise the IVIG demand among paediatric and adult patients in Hospital USM and subsequently provides an objective measurement for IVIG usage according to its indications. A better understanding of IVIG usage will contribute towards the improvement of IVIG therapy prescriptions for appropriate patients.

1.5 Research questions

1. What are the characteristics of IVIG demand in Hospital Universiti Sains Malaysia?
2. What are the labelled indications for IVIG usage in patients in Hospital Universiti Sains Malaysia?
3. What are the off-label indications for IVIG usage in patients in Hospital Universiti Sains Malaysia?
4. Is there any difference in indications of IVIG demand among paediatric patients compared to adult patients?

CHAPTER TWO:

OBJECTIVE

CHAPTER TWO

2.1 General objective

To determine the characteristic of IVIG demand in Hospital Universiti Sains Malaysia.

2.2 Specific objective

1. To determine the labelled indications of patients receiving IVIG in Hospital Universiti Sains Malaysia.
2. To determine the off-label indications of patients receiving IVIG in Hospital Universiti Sains Malaysia.
3. To compare the labelled and off-label use of IVIG among patients in Hospital Universiti Sains Malaysia.

2.3 Alternative hypotheses

1. There is an association between the patient's demographic (age, sex, and race) with selected factors (labelled and off-label usage).
2. There is an association between the category of indications with selected factors (label and off-label usage).

2.4 Null hypothesis

1. There is no association between the patient's demographic (age, sex, and ethnicity) with selected factors (labelled and off-label usage).

2. There is no association between the category of indication with selected factors (labelled and off-label usage).

CHAPTER THREE:

METHODOLOGY

CHAPTER THREE

METHODOLOGY

3.1 Study background

This study focused on the characteristic of IVIG demand among paediatric and adult patients in Hospital Universiti Sains Malaysia (USM). This study also compares the labelled and off-label indications for IVIG among paediatric and adult patients in Hospital USM.

3.2 Study design

This retrospective cross-sectional study used the original IVIG request list from the Pharmacy Department and patients' case note review in the Hospital USM Medical Record Unit.

3.3 Study area

This study was conducted at Hospital USM. It is the teaching hospital for the Universiti Sains Malaysia's School of Medical Sciences. The hospital is equipped with 829 beds and serves as a tertiary referral centre, mainly for the East Kelantan and North Terengganu districts as well as for other government and private hospitals on the East Coast of Malaysia.

The hospital is equipped with comprehensive medical facilities and offers various speciality and subspeciality services, which attract numerous patients with various diseases to seek treatment at this hospital. This hospital also serves as a regional referral centre for adult haematological stem cell transplantation on the East Coast of Malaysia.

3.4 Study population

All paediatric (age under 18 years old) and adult patients who had been prescribed IVIG beginning the 1st of January 2019 until the 31st of December 2020 were identified and included. The list of patients was obtained from the requests for IVIG filed within the Pharmacy Department of the Hospital USM.

3.5 Subject criteria

3.5.1. Inclusion criteria

i. All paediatric (age under 18 years old) and adult patients who had been prescribed IVIG.

3.5.2. Exclusion criteria

i. Incomplete receipt of IVIG therapy.
ii. Incomplete data in the request list for IVIG or incomplete documentation.
iii. Missing data or case notes.

3.6 Sample size

The single proportion formula was used to calculate the sample size.

Specific objective 1: To determine the labelled indications of patients receiving IVIG in Hospital Universiti Sains Malaysia.

Single proportion, $n = t^2 \times p(1-p)/m^2$

Where, *n* = sample size required

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of labelled use of IVIG

m = margin of error at 10% (standard value of 0.1)

Based on Toh, C.C, et al. (2018), the prevalence of IVIG usage for Kawasaki disease according to the FDA-approved indication in Universiti Kebangsaan Malaysia Medical Centre was 27%. This study wished to estimate the proportion of patient number who received IVIG in Hospital Universiti Sains Malaysia within 10% of the true patient number with a 95% confidence interval. The minimum sample size required with an additional 20% non-response rate is:

$n = 1.962 \times 0.27(1 - 0.27)/0.12$

$n = 3.84 \times 0.27(1 - 0.27)/0.12$

$n = 3.84 \times 0.20/0.01$

$n = 77$

77 + drop out 20%

77+15 = 92.

Specific objective 2: To determine the off-label indications of patients receiving IVIG in Hospital Universiti Sains Malaysia.

Single proportion, $n = t^2 \times p(1-p)/m^2$

Where, *n* = sample size required

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of off-label use of IVIG

m = margin of error at 10% (standard value of 0.1)

Based on Toh, C.C, et al. (2018), the prevalence of IVIG usage for neonatal jaundice as an off-label indication in Universiti Kebangsaan Malaysia Medical Centre was 27%. This study wished to estimate the proportion of patient number who received IVIG in Hospital Universiti Sains Malaysia within 10% of the true patient number with a 95% confidence interval. The minimum sample size required with an additional 20% non-response rate is:

$n = 1.962 \times 0.27(1 - 0.27)/0.12$

$n = 3.84 \times 0.27(1 - 0.27)/0.12$

$n = 3.84 \times 0.20/0.01$

$n = 77$

77 + drop out 20%

77+15 = 92.

Specific objective 3: To compare the labelled and off-label use of IVIG among patients in Hospital Universiti Sains Malaysia.

Single proportion, $n = t^2 \times p(1-p)/m^2$

Where, *n* = required sample size

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of patients receiving IVIG

m = margin of error at 10% (standard value of 0.1)

Based on Toh, C.C, et al. (2018), the proportion of IVIG usage for the male gender in Universiti Kebangsaan Malaysia Medical Centre was 56.5%. This study wished to estimate the population proportion in Malaysia with a level of significance of 0.05 and power of 80%. The minimum sample size required with an additional 20% non-response rate is:

$n = t^2 \times p(1 - p)/m^2$

$n = 1.962 \times 0.56(1 - 0.56)/0.12$

$n = 3.84 \times 0.56(1 - 0.56)/0.12$

$n = 3.84 \times 0.25/0.01$

$n = 96$

96 + drop out 20%

96 + 19 = 115

Conclusion

The biggest sample size based on the calculation from the each of the objectives is 115 from the third objective. Hence, the final sample size for this study is 115.

3.7 Sampling method and subject recruitment

3.7.1. Sampling method

Purposive sampling was employed as patients who received IVIG from the request list were recruited as subjects.

3.7.2. Subject recruitment

Target population: Patients who were prescribed IVIG in Hospital Universiti Sains Malaysia.

Sampling frame: Taken from the IVIG request list in the Pharmacy Department of the Hospital USM.

3.8 Research tool

The patient's proforma was prepared to ensure complete data collection and easy to be reviewed (Appendix A). The data included were:

i. Patient's identification number.

ii. Department.

iii. Age.

iv. Sex.

v. Race.

vi. Weight.

vii. Date of usage.

viii. Diagnosis (labelled use).

ix. Diagnosis (off-label use).

x. Dosage of IVIG.

xi. Frequency.

xii. Dosage of IVIG used.

xiii. Patient's medical record.

3.9 Data collection method

The Hospital Director and the Hospital USM Pharmacy Department were approached to get approval and written consent to conduct this research at Hospital USM. Patient's details were identified using the request list from the Hospital USM Pharmacy Department. The patient case notes were then reviewed in the Hospital USM Medical Record Unit. The principal investigator (registered medical officer) recorded all the information and parameters in the patient's proforma form.

3.10 Statistical analysis

IBM SPSS version 26 for Windows software was used for data entry and analysis. The data were analysed using descriptive and inferential analyses.

Descriptive analysis was done for general objective, specific objectives 1 and 2, to determine the prevalence and indications of IVIG for labelled and off-label use in Hospital USM.

Independent sample T-test and Chi-squared test were done for specific objective 3, to compare the labelled and off-label use of IVIG between adults and paediatric patients. The significance level was set at a p-value of less than 0.05.

3.11 List of variables

3.11.1 Dependant variables

labelled and off-label IVIG usage.

3.11.2 Independent variables

age, sex, race, and indication of IVIG.

3.12 Variables definition

Age

The patient's age is defined as the year from the date of birth as per recorded in the patient's registration record.

Sex

The sex of the patient (male or female) is determined as per recorded in the patient's registration record.

Race

The patient's race (Malay, Chinese, Indian, Siamese, or others) is determined as per recorded in the patient's registration record.

Labelled IVIG indication

Labelled IVIG indication is defined as clinical indications for which IVIG have been licensed by the US Food and Drug Administration (FDA).

Off-label IVIG indications

Off-label IVIG indication is defined as indications for which no manufacturer has filed an application with the Food and Drug Administration (FDA).

3.13 Ethical issue

3.13.1 Ethical approval

Ethical approval (USM/JEPeM/21080540) was acquired from the Human Research Ethics Committee (HREC) of Universiti Sains Malaysia.

3.13.2 Subject vulnerability

All adult and paediatric patients who were prescribed IVIG therapy in the Hospital USM within the period of study were identified from the list of requests for IVIG filed within the Department of Pharmacy and their case notes were reviewed by the principal investigator. The information obtained was recorded anonymously in the proforma before being analysed by the principal investigator. There was no direct encounter or approach by the principal investigator with the subjects during data collection. No informed consent is taken from the patients or the guardians for the paediatric patients as all the data collection were done anonymously.

3.13.3 Conflict of interest

There was no conflict of interest by researchers in this study.

3.13.4 Privacy and confidentiality

Identifiable information such as name, registered identification number, and residence address of the subjects were not collected to protect their privacy and confidentiality. They were given unique reference numbers in the proforma and their proforma were attached with these reference number to ascertain their confidentiality throughout this study. The proforma were secured in a locked locker and only the research team

members were granted access to the data. The data obtained from the study will be deleted following the designated storage duration.

3.13.5 Community sensitivities and benefit

The findings from the study may benefit the community as evidence of the characteristics of intravenous immunoglobulin utilisation in a teaching hospital. The data provided are useful for hospital administrators to plan for a more proper drugs and pharmaceutical expenditure especially for the IVIG and its distribution in the hospital. The data could also be used to develop a comprehensive protocol or guideline as a reference for clinicians when prescribing IVIG therapy to patients. The data could also be used for the surveillance of IVIG usage in the hospital and serves as a basis to develop a national registry for patients who received IVIG therapy in the future.

3.13.6 Honorarium and incentives

No honorarium was given as no subject was approached in person.

3.13.7 Other ethical review board approval

Not applicable.

3.14 Study flowchart