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Access and use of immunoglobulins in secondary supportive cancer care: A systematic literature review

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Abstract

Background: Immunoglobulin replacement therapy (IgRT) benefits patients with primary immuno deficiency (PID) originating from the innate or polygenic defects in the immune system. However, evidence supporting their therapeutic role is not as explicit in secondary immuno deficiency (SID) resulting from the treatment of haematological malignancies.
Objectives: This study aimed to (1) create a dataset of relevant research papers, which explore the use of IgRT in SID for analysis, (2) assess the risk of bias within this dataset and (3) study the characteristics of these papers.
Design: This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. In addition to the risk of bias, the study characteristics explored in this article included study design, study geographical location and year of publication.
Data Sources and Methods: To identify studies relevant to the research question, EMBASE and PubMed databases were searched. The Population, Intervention, Comparison and Outcome (PICO) framework was used to assess study quality. Risk of bias and quality of studies were assessed in accordance with the study design. As one model was not appropriate to assess bias in all articles, several tools were used.
Results: A total of 43 studies were identified from the literature search as relevant to the research objective. The most common study design was a retrospective case–control cohort study ($n = 16/43$), and randomised trials were among the least commonly used approaches ($n = 1$). Research in this area is occurring around the globe including the United States ($n = 7$), Italy ($n = 7$), China, India, Japan and throughout Europe. The annual number of papers in this area has varied from 2012 ($n = 1$) to 2021 ($n = 7$). The studies in this article demonstrated a varied risk of bias, with 9 of the 20 cohort studies scoring less than 5 out of 9 stars.
Conclusions: Randomised controlled trials are less frequently used to assess access and use of immunoglobulins. More commonly, a retrospective case–control cohort study was used which correlates with the higher risk of bias seen in the studies in this article. Most of the research concerning immunoglobulin use and access occurs in higher-income countries.

Keywords

Immunoglobulin, use, access, research, systematic review

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Introduction

Background

Antibody deficiency (AD) disorders are broadly classified as a group of immunodeficiencies whereby the individual is incapable of producing an effective antibody response to a pathogen. Clinically, AD is primarily characterised by recurring infections and can be diagnostically confirmed by a marked decrease in serum immunoglobulin G (IgG) level.[1] AD can be further indexed according to its aetiology as a primary or secondary immuno deficiency (PID or SID, respectively) with significant predominant occurrence of the latter in the general population.[2]

Primary Immuno Deficiencies (PIDs) are disorders originating from the innate or polygenic defects in the immune system in which a crucial component, immunoglobulin synthesis and function, is impaired due to abnormalities in differentiation or function of B lymphocytes.[1] The clinically significant PID includes rare diseases, such as X-linked agammaglobulinea (XLA) or autosomal recessive agammaglobulinemia and difficult to diagnose common variable immunodeficiency, among other diseases. In contrast, individuals with SID are not initially predisposed to AD, rather they develop this abnormality as a result of certain clinical conditions due to various aetiologies, such as malnutrition, infections targeting the immune system (e.g. HIV), malignancy or due to specific medications negatively impacting the immune system.[2-5] Pertaining to this review, both solid tumours and haematologic malignancies can result in low-serum antibody levels, hypogammaglobulinemia, whether it manifests as disease-related condition, or iatrogenic secondary disorder caused by treatments, such as B cell-targeted therapies, steroids, immunosuppressive agents and radiation.[2-5]

In the absence of treatment, SID can lead to organ damage, immune dysfunction, recurring infections, morbidity and mortality. The most common haematologic cancers, such as multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL), have high incidences of infection-related mortality, with reports of up to 65% in CLL being infection-related.[6]

Currently, first-line treatment of recurring infections in SID strongly favours prophylactic antibiotic administration, such as macrolide antibiotics or co-trimoxazole.[7] However, a recent systematic review on the efficacy of antibiotic prophylaxis conducted by Egan et al.'s[8] study has called for updated clinical guidelines to facilitate prophylactic antibiotic decision-making. These findings coupled with the high rate of mortality in haematological cancers require close examination of alternative strategies, beyond antibiotics, to treat this vulnerable patient group.[6,8]

Immunoglobulin replacement therapy (IgRT) is a well-established treatment in PID patients with ADs. Its mechanism of action is complex, modulating Fc receptor function, regulating T cell and B cell function and providing antibodies with a broad spectrum of specificities against various pathogens.[9,10] To define the clinical outcomes of IgRT in SID, one must consider the following definitions used by the European Medicines Agency (EMA). The primary endpoint of immunoglobulin use is defined as a reduction in serious bacterial infections (SBI); these are defined as 'bacteraemia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia or visceral abscess' with secondary parameters relying on pharmacokinetic measures of serum Ig, reduction in antibiotic prescription, hospitalisation and all other infections.[11] Hence, this knowledge can be applied to SID as a determinant of the efficacy of treatment.

Despite SID being a licensed indication for IgRT by major regulators, such as the EMA, its utilisation in supportive cancer therapy and the validity of use in the current licensed indications are not sufficiently documented.[12–14] Access to immunoglobulin therapies relies on the availability of human plasma for its manufacture, meaning that production cannot be increased easily. With a projected 6%–8% annual increase in immunoglobulin usage, it is crucial to be informed about the best practices regarding the frequency of IgRT use and access in patients with haematological malignancies (HMs).[15]

***Aim*:** To better understand the characteristics of studies in the area of immunoglobulin use and access and create a dataset of studies for future thematic analysis.

Objectives

1. To understand the most common research designs adopted and participating patient numbers in each study;
2. To understand the frequency of research into immunoglobulin use and access;
3. To understand which countries are conducting research in this area;
4. To understand the risk of bias (RoB) present in research in this area.

Methodology

Overview

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[16] (Appendices, Supplementary Checklist). The exclusion and inclusion criteria for the systematic search strategy were selected by the research team which included academic and industry experts.

A literature search was conducted to identify articles concerning the use of immunoglobulins in supportive cancer treatments for those with SID. Specific focus was placed on HMs due to preliminary research outlining the benefit of immunoglobulin support therapy in this cohort.

The present review used a quantitative approach to address the research questions. The primary endpoint of this review was to establish the current body of scientific knowledge on IgRT in HMs in the previous 10 years (February 2012–February 2022), with a focus on the use and access to therapies.

Search strategy

Search terms were comprehensive and focused on the core domains of the topic, namely the following key concepts (1) immunoglobulins, (2) haematological neoplasms and (3) secondary immune deficiencies, and their synonyms. The main objectives of this review were aligned with immunoglobulin use; hence, these concepts served as an 'anchor' for the search. Accordingly, only articles with 'immunoglobulin' mentioned in the title or abstract were included. The search strategy composed by Raanani et al.[6] was used to support the development of a search string for immunoglobulin and HMs; synonyms and alternate spellings of identified terms were used alongside the extraction of terms from relevant articles recommended by a clinical expert in the field.[2,5,13,15,17–19]

Brand names for human immunoglobulin were identified from FDA and EMA electronic databases for licensed human blood products.[14,19] A clinical expert (L.C.) from the Plasma Protein Therapeutics Association (PPTA) provided feedback and suggestions on keywords to include or exclude, and the search string was peer-reviewed prior to final abstract screening. Inclusion of key terms such as 'infection' and 'prophylaxis' were considered, but these terms were agreed to be beyond the scope of this review.

Consequently, the search string was applied with slight variation to encapsulate the specific requirements and features of each database. The full search strategies used for each database are provided in the Appendices (Supplemental Appendices 1–3). All search results were limited to those in English and where the full text was available.

Data sources

The search strategy was applied to both Excerpta Medica Database (EMBASE) and PubMed electronic databases. Manual searching of reference sections from included papers was conducted to identify subsequent relevant material that was not captured in the initial search; however, no suitable reports were retrieved.

Study selection criteria

The aim of the search was to identify all relevant studies that investigated the use of immunoglobulins in supportive HM therapy and were published in the past 10 years on account of relevance and current guidelines.

Inclusion criteria. The population, intervention, comparison and outcome (PICO) approach was used for study inclusion.[20] The population of interest were patients with haematological cancers who experienced SID because of this malignancy. The intervention was immunoglobulin therapy (intravenous (IVIG), intramuscular (IMIG) or subcutaneous (SCIG)) irrespective of treatment duration or dosage. The comparison group was either placebo or standard treatment. Outcome measurements were broad and included increased IgG levels, unresponsiveness, recurrence of infection or patient-reported measures of improved quality of life. However, the primary outcome to measure was the potential expansion of immunoglobulin utilisation in haematological cancer treatment and the assessment of the global demand of human plasma to support this.

The types of studies included in this review were randomised control trials, case–control studies, systematic reviews and meta-analyses, and cohort studies and articles; all of which were peer-reviewed.

Exclusion criteria. Research such as incomplete studies, study protocols, commentary, animal studies, in vitro or ex vivo case studies and studies that were not peer-reviewed were excluded. Studies unavailable in English or those without an available full text article were excluded. Those with a sole focus on monoclonal antibodies and immunoglobulin for indications other than HMs were excluded due to a lack of relevance to the research question.

Study selection process

Citations of all identified studies were imported into Zotero citation software and duplicates removed. Initial screening of titles was carried out and those that were evidently irrelevant to the proposed objectives were removed. Subsequently, titles and abstracts were screened using Covidence®, and full texts were selected for inspection. The full text of each identified study was screened against predetermined inclusion and exclusion criteria by one reviewer. The reviewers were not blind to authorship or journals in which the articles were published. Study selection was performed by M.C. Where there was a confusion regarding eligibility, the study was discussed with B.D.N. to confirm inclusion or exclusion.

Data extraction

A data extraction form was constructed based on the Cochrane Checklist[21] and on the objectives of the research question to include information pertaining to authors, geographical location of the study, study design, immunoglobulin utilisation, haematological cancer assessed, sample size (where applicable), patient outcomes, expert opinions or commentary relating to immunoglobulins. The primary

outcome of interest was trends in immunoglobulin use in supportive HM treatment over the past decade. The related quantitative findings were extracted.

Data synthesis

Any recurring quantitative measures were considered for statistical analysis. Synthesised data were interpreted under the main aims of this review and counts of included studies were tabulated for clarity and ease of comparison.

Study of risk of bias (RoB) and quality assessment

RoB and methodological quality assessment (QA) tools were chosen as recommended by Ma et al.[22] based on the study design and were applied to all screened articles which fulfilled the criteria of the tools used. For systematic reviews, AMSTAR-2 was used;[23] the Newcastle–Ottawa tool was used for cohort studies;[24] the JBI tools were used for quasi-experimental studies and for case reports;[25] the CASP Checklist was used for qualitative studies.[26] These tools were used to examine bias in the methodological quality of the articles. Those failing the QA stage were excluded from further thematic analysis.

Results and discussion

Study selection

A flow diagram representing the study identification and selection procedure is shown below in Figure 1. The initial search of PubMed and EMBASE yielded a total of 227 articles for screening after removal of duplicates. Among these 227 articles, 141 articles were excluded following abstract and title screening. Full text assessment was carried out on 86 articles. Exclusion criteria were applied, and 43 studies were excluded at this stage due to a lack of relevance to the research question, incorrect patient cohorts or interventions, or ongoing trials that had no relevant results published as of yet. A total of 43 articles were selected for RoB, QA and thematic analysis.

Study design

A total of 43 articles relevant to the topic of IgRT in HMs were identified within the period of 2012–2022. Of these articles, 4 were qualitative studies,[12,27–29] 10 were narrative literature syntheses which featured expert opinions,[17,30–38] 1 was a systematic review,[39] 15 were retrospective case-controlled cohort studies,[40–53,67] 1 was a non-randomised control trial,[54] 1 was a mixed-methods cohort study,[55] 4 were case reports,[56–59] 6 were prospective case-controlled studies[60–65] and 1 was a randomised placebo-controlled trial[66] (Figure 2). On first glance, it could be argued that these data demonstrate a lack of rigour in the studies conducted; however, in reality, the study of medicine use and access is often best investigated using cohort studies as they provide a realistic source of data and are more cost-effective and cause less disruption to healthcare provision than randomised control trials.

Research outputs

It is also worth noting the distribution of years of publication as shown in Figure 3 which indicates an increase in publications, an indication of growing importance and interest in this field of medicine.

Geographical location

The majority ($n = 29$) of studies confined their results to a single country or continent (the United States, Australia, India, Japan, China and several countries in Europe). The most productive countries in terms of research output were the United States and Italy. The geographical location of these studies is visualised in Figure 4; a total of 14 studies were excluded from geographical analysis due to missing data on a specific geographical location or those which were narrative literature synthesis and hence, were not tied to a single location. This trend is likely due to especially active research groups in this area of study within these countries.

The characteristics of the studies assessed are shown in Supplemental Table B. Of the studies assessing specific HMs and not HM as a general disease ($n = 18$), CLL, MM and non-Hodgkin's lymphoma (NHL) were most commonly analysed conditions in the same paper, however, there were also single studies that included patient with chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), Hodgkin's lymphoma (HL), follicular lymphoma (FL) and Waldenström macroglobulinemia (WM). The frequency of the different types of HM occurrence in studies is shown in Figure 5. Some studies included multiple conditions. The majority of studies ($n = 22$) had an exclusive focus on SID and immunoglobulin use in cancer.[12,17,30,32–35,37–39,43,47–49,51,53,57,58,60–64,66] Others focused on topics, such as clinicians' opinion of SID and its' management and diagnosis.[27–29] Three studies placed a specific focus on immunoglobulin withdrawal[31,44,54] and six studies considered factors causing an increase in the incidence of Hypogammaglobulinemia (HGG) in HM, such as chemotherapy.[36,45,50,56,59,65]

RoB and QA results

The selected studies which could be screened using RoB and QA tools according to their study design were screened (31 out of 42). Some were not screened using an

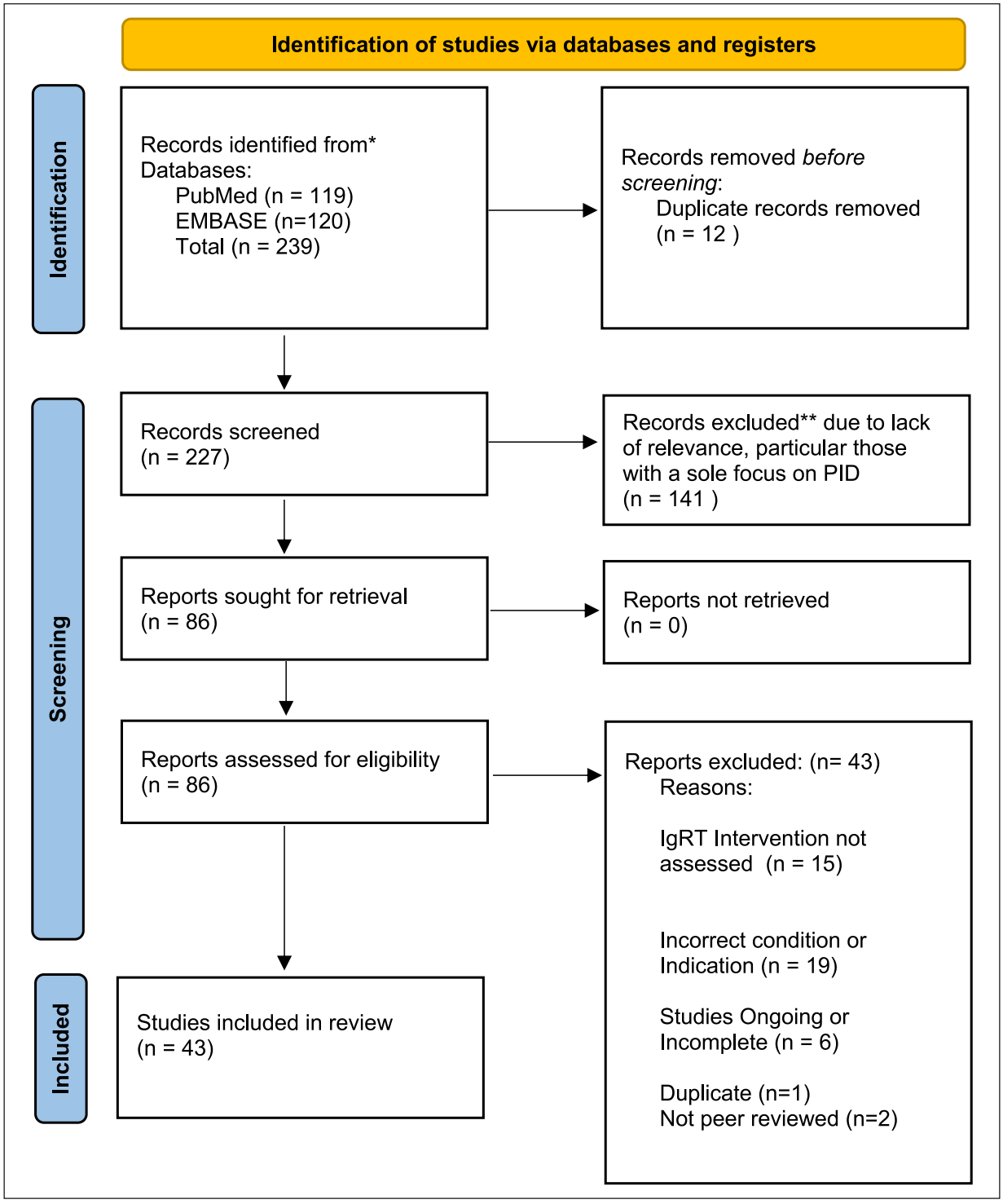

Figure 1. PRISMA flow diagram detailing study identification and selection procedure.

RoB tool due to their study design, for example, case reports and qualitative studies. The tools and the achieved scores are expanded below (Supplemental Appendices: Table A. RoB Assessment Results). Of the 31 studies assessed, there was a high variation in the RoB and overall quality of the article. As an example, of the cohort studies, 9 out of 20 studies scored less than 5 stars out of a total of 9 stars, indicating a high RoB (45.0%).

Tools such as JBI Critical Appraisal Tool and CASP listed specific elements that should be present to fulfil a study with high quality and low RoB. Hence, the results of these tools did not translate to a quantitative measure but

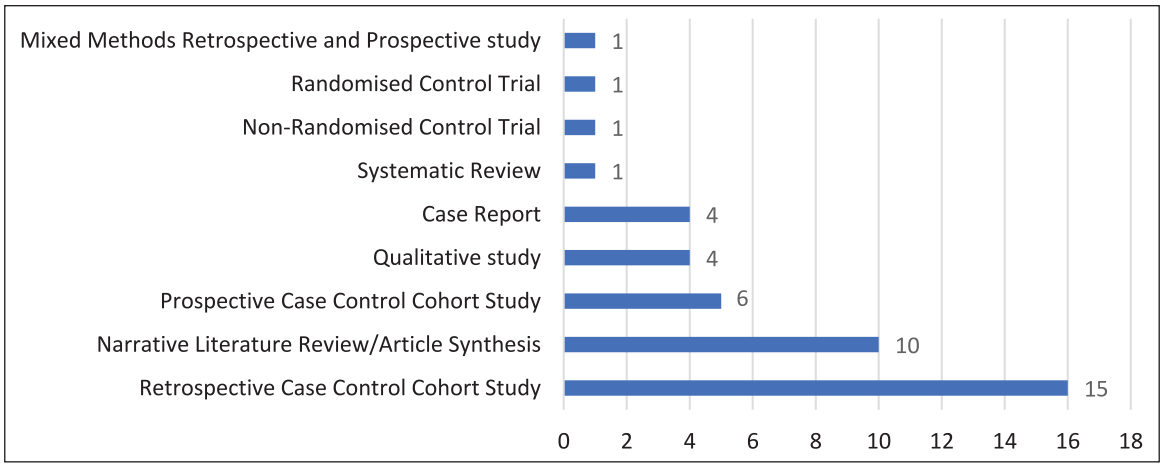

Figure 2. Types of studies included in systematic review.

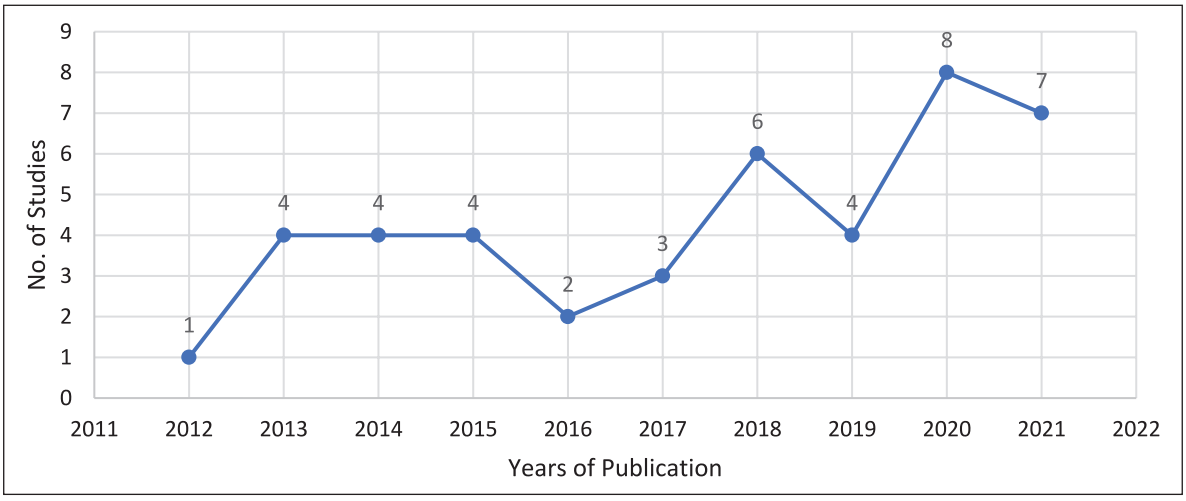

Figure 3. Years of publication of included studies.

rather these studies did not have any critical elements missing that would indicate a very high RoB. However, considering the evidence level of qualitative surveys as compared to randomised control trials, it can be assumed that due to the inherent limitations of design, there is an underlying higher RoB present.[68]

Patient numbers and malignancy type

The total number of patients assessed ranged from a single patient in case studies to up to 9253 patients.[33] Patient populations varied greatly due to heterogeneity in underlying HM, criteria for IgRT initiation or withdrawal and treatment route. Of the 43 studies, 32 included an assessment of patients. In total, 10,586 patients were included in the studies assessing patients and immunoglobulin use or methods to identify SID in HM. Some studies related to a single type of HM or multiple sub types (Figure 5).

Limitations and future research

This systematic literature review had several limitations. First, it was limited to articles written in English only and covered the timeframe of the previous 10 years. Comparisons of studies were hindered in many aspects due to heterogeneity between the HM assessed, definitions of HGG and patient characteristics. Western countries represented the majority, possibly since IgRT is more commonly used there. Furthermore, this study was restricted to examination of use and access and did not necessarily consider clinical benefits, patient-reported outcomes and statistical analyses of IgRT success in all studies.

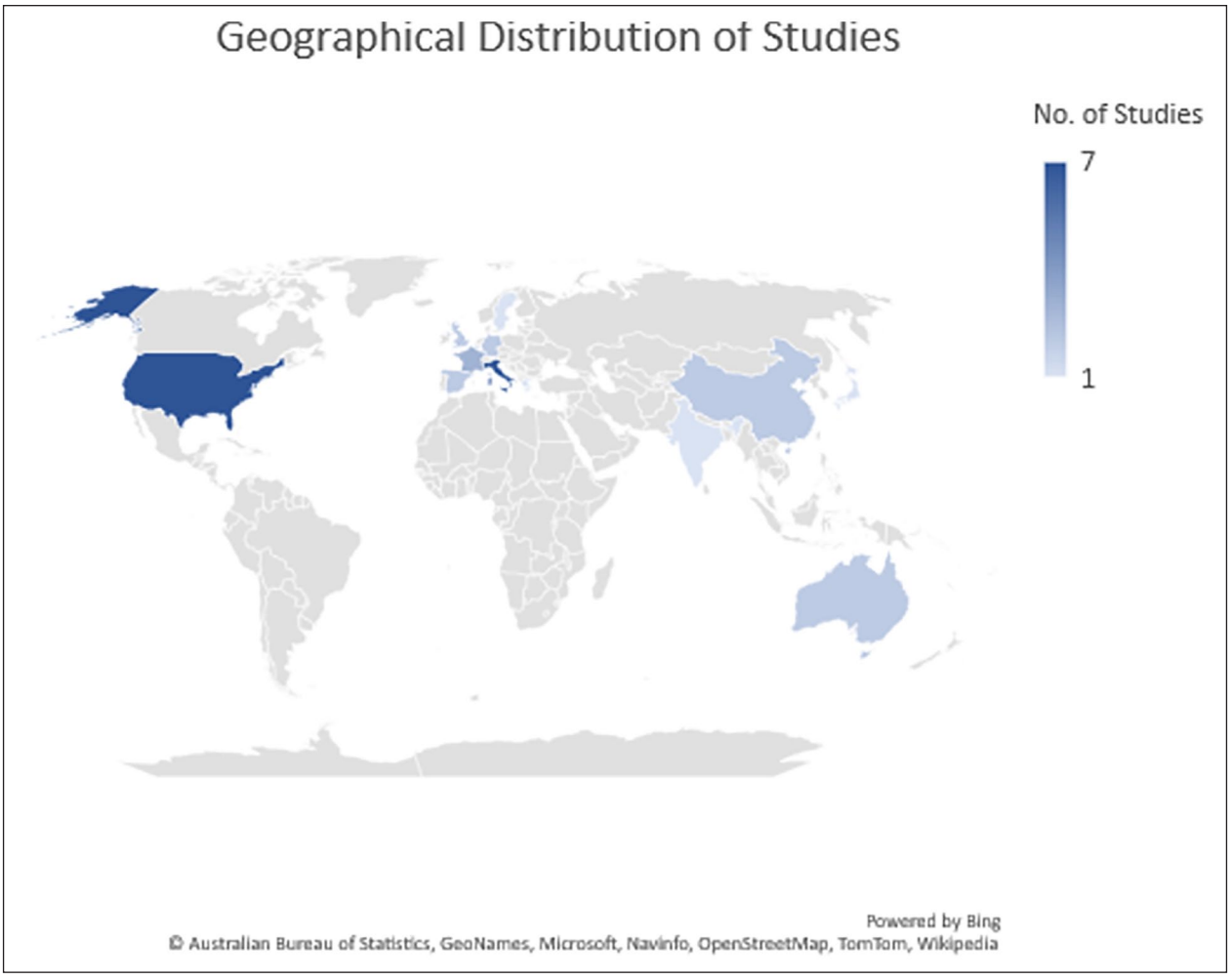

Figure 4. Geographical location of included studies.
Geographical location: China ($n = 2$),[27,46] France ($n = 3$),[34,48,64] Oceania – Australia/New Zealand ($n = 2$),[29,40] United States ($n = 7$),[43,45,52–54,58,63] Italy ($n = 7$),[33,41,47,49,50,66,67] Sweden ($n = 1$),[55] Japan ($n = 1$),[56] Spain ($n = 2$),[35,42] United Kingdom ($n = 2$),[44,61] Germany ($n = 2$),[60,62] Belgium ($n = 1$),[37] Greece ($n = 1$)[51] and India ($n = 1$).[65]

Future research could include an investigation into the link between the clinical effects of IgRT and IgRT access and use. This link could be compared between higher- and lower-income countries, or between countries that use traditional IVIG more commonly and those that do not.

Conclusions and recommendations

The healthcare community is increasing their efforts in the research of immunoglobulin use and access. However, they could build on the success seen in the United States and Italy to contribute further resources and efforts to better understand immunoglobulin access and use in both lower- and higher-income countries. The reliability of these studies may benefit from being more rigorous in their research designs. However, it is important to ensure that in pursuit of rigour, we do not lose the richness of data and understanding that is achieved through qualitative research. The analysis included in this report is aimed to set the stage for further studies to address the global access and appropriate use of IgRT in HM. Such studies could include qualitative research performed on this dataset to understand more about issues concerning medicine access and use. Healthcare professionals (HCP), regulators, payers and policymakers should realise that this is an ever-growing and ever-changing field of medicine and that the prevalence of HGG in HM is only likely to increase, putting pressure on Immunoglobulin access. Hence, now is the time to invest resources into addressing the topic of immunoglobulin use, so that patients can continue to access IgRT as a supportive cancer treatment in HM.

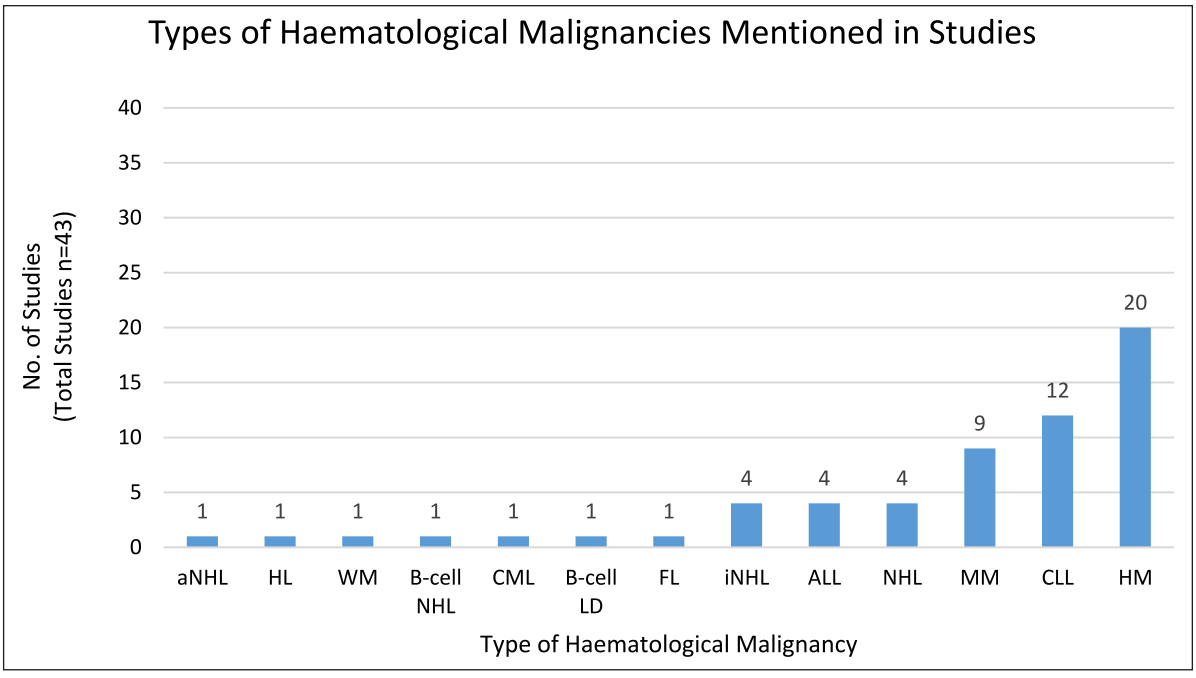

Figure 5. Types of HM assessed.

Authors' note

Covidence screening information and data extraction forms and template can be viewed upon request.

Declarations

Ethics approval and consent to participate

Not applicable. This study did not require ethical approvals as it did not involve human participants.

Consent for publication

Not applicable.

Author contributions

Muireann Counihan: Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing.
Larisa Cervenakova: Conceptualization; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.
Dominika Misztela: Conceptualization; Resources; Supervision; Writing – review & editing.
Maarten Van Baelen: Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.
Bernard D Naughton: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

Bernard Naughton is an Associate Editor of The Journal of Medicine Access and an author of this paper; therefore, the peer-review process was managed by alternative members of the board and the submitting editor was not involved in the decision-making process. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

All data used in this study have been provided.

Registration

This study was not registered with PROSPERO/INPLASY. This project was short in duration and did not have available resources to first register the study in advance of the study start date.

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Supplemental material

Supplemental material for this article is available online.

References

1. Pimenta FMCA, Palma SMU, Constantino-Silva RN, et al. Hypogammaglobulinemia: a diagnosis that must not be overlooked. *Braz J Med Biol Res* 2019; 52(10): e8926.

2. Patel SY, Carbone J and Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. *Front Immunol* 2019; 10: 33.
3. .Wood P, Stanworth S, Burton J, et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Exp Immunol 2007; 149(3): 410–423.
4. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 2017; 139(3S): S1–S46.
5. Patel V and Cowan J. Discontinuation of immunoglobulin replacement therapy in patients with secondary antibody deficiency. *Exp Rev Clin Immunol* 2020; 16(7): 711–716.
6. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. *Cochr Datab Syst Rev* 2008(4): CD006501.
7. Srivastava S and Wood P. Secondary antibody deficiency: causes and approach to diagnosis. *Clin Med* 2016; 16(6): 571–576.
8. Egan G, Robinson PD, Martinez JPD, et al. Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: a systematic review of randomized trials. *Cancer Med* 2019; 8(10): 4536–4546.
9. Bayry J, Misra N, Latry V, et al. Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. *Transfus Clin Biol* 2003; 10(3): 165–169.
10. Privigen 100mg/ml solution for infusion: summary of product characteristics (SmPC) – (emc) [Internet], https://www.medicines.org.uk/emc/medicine/21359#PHARMACOLOGICAL_PROPS (accessed 7 February 2022).
11. European Medicines Agency (EMA). Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (Report no: EMA/CHMP/BPWP/94033/2007 rev. 4) [Internet]. EMA, 2021, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-4_en.pdf
12. Jolles S, Michallet M, Agostini C, et al. Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus. *Eur J Haematol* 2021; 106(4): 439–449.
13. European Medicines Agency (EMA). Clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) [Internet]. *EMA*, 2018, https://www.ema.europa.eu/en/clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig (accessed 3 February 2022).
14. Immune globulins, FDA [Internet], https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins (accessed 3 February 2022).
15. Prevot J and Jolles S. Global immunoglobulin supply: steaming towards the iceberg? PubMed, https://pubmed.ncbi.nlm.nih.gov/33044340/ (accessed 3 February 2022).
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
17. Agostini C, Blau IW, Kimby E, et al. Prophylactic immunoglobulin therapy in secondary immune deficiency – an expert opinion. *Expert Rev Clin Immunol* 2016; 12(9): 921–926.
18. Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus - PubMed [Internet]. [cited 2022 Feb 3]. Available from: https://pubmed.ncbi.nlm.nih.gov/33453130/
19. European Medicines Agency (EMA). Medicines [Internet]. EMA, https://www.ema.europa.eu/en/medicines (accessed 3 February 2022).
20. Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995; 123(3): A12–3.
21. Data extraction forms [Internet], https://dplp.cochrane.org/data-extraction-forms (accessed 21 February 2022).
22. Ma LL, Wang YY, Yang ZH, et al. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Milit Med Res* 2020; 7(1): 7.
23. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358: j4008.
24. Lo CKL, Mertz D and Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014; 14(1): 45.
25. Site home page. Joanna Briggs Institute [Internet], https://jbi.global/ (accessed 7 March 2022).
26. Brice R. CASP – Critical Appraisal Skills Programme: CASP Checklists [Internet], https://casp-uk.net/casp-tools-checklists/ (accessed 7 March 2022).
27. Ye C, Liu J, Song X, et al. A clinician survey for management of the secondary immunodeficiency caused by hematological malignancies in China. *Medicine* 2021; 100(3): e23935.
28. Na IK, Buckland M, Agostini C, et al. Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies. *Eur J Haematol* 2019; 102(6): 447–456.
29. Wong J, Wood EM, Crispin P, et al. Managing hypogammaglobulinaemia secondary to haematological malignancies in Australia and New Zealand: a clinician survey. *Intern Med J* 2019; 49(3): 358–363.
30. Dhalla F, Lucas M, Schuh A, et al. Antibody deficiency secondary to chronic lymphocytic leukemia: Should patients be treated with prophylactic replacement immunoglobulin. *J Clin Immunol* 2014; 34(3): 277–282.
31. Patel V and Cowan J. Discontinuation of immunoglobulin replacement therapy in patients with secondary antibody deficiency. *Expert Rev Clin Immunol* 2020; 16: 711–716.
32. Seppänen M. Immunoglobulin G treatment of secondary immunodeficiencies in the era of novel therapies. *Clin Exp Immunol* 2014; 178(Suppl. 1): 10–13.
33. Girmenia C, Cavo M, Offidani M, et al. Management of infectious complications in multiple myeloma patients: expert panel consensus-based recommendations. *Blood Rev* 2019; 34: 84–94.
34. Mouthon L, Fermand JP and Gottenberg JE. Management of secondary immune deficiencies: what is the role of immunoglobulins. *Curr Opin Allergy Clin Immunol* 2013; 13(Suppl. 2): S56–S67.
35. Sánchez-Ramón S, Bermúdez A, González-Granado LI, et al. Primary and secondary immunodeficiency diseases in oncohaematology: warning signs, diagnosis, and management. *Front Immunol* 2019; 10: 586.

36. Christou EAA, Giardino G, Worth A, et al. Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab. *Int Rev Immunol* 2017; 36(6): 352–359.
37. De Meester C, Bourgeois J, Devriese S, et al. Unraveling the mystery of polyvalent immunoglobulins in Belgium: do we have an indication? *Int Arch Allergy Immunol* 2021; 182: 1127–1134, https://www.embase.com/search/results?subaction=viewrecord&id=L2013576144&from=export
38. Dhalla F and Misbah SA. Secondary antibody deficiencies. *Curr Opin Allergy Clin Immunol* 2015; 15(6): 505–513.
39. Monleón Bonet C, Waser N, Cheng K, et al. A systematic literature review of the effects of immunoglobulin replacement therapy on the burden of secondary immunodeficiency diseases associated with hematological malignancies and stem cell transplants. *Expert Rev Clin Immunol* 2020; 16(9): 911–921.
40. Hoo T, Lim EM, John M, et al. Calculated globulin as a screening tool for hypogammaglobulinaemia or paraproteins in hospitalized patients. *Ann Clin Biochem* 2021; 58(3): 236–243.
41. Mauro FR, Morabito F, Vincelli ID, et al. Clinical relevance of hypogammaglobulinemia, clinical and biologic variables on the infection risk and outcome of patients with stage A chronic lymphocytic leukemia. *Leuk Res* 2017; 57: 65–71.
42. Ochoa-Grullón J, Benavente Cuesta C, Pérez López C, et al. Evaluation of polysaccharide typhim Vi antibody response as a predictor of humoral immunodeficiency in haematological malignancies. *Clin Immunol* 2020; 210: 108307.
43. Lange CS, Rahrig A, Althouse SK, et al. Hypogammaglobulinemia in adolescents and young adults with acute lymphoblasticl. *J Adolesc Young Adult Oncol* 2020; 9(6): 687–692.
44. Goddard S, Hughes D, Diwakar L, et al. Impact of stopping long-term immunoglobulin therapy in haematological secondary antibody deficiency. *Br J Haematol* 2020; 189: 91.
45. Casulo C, Maragulia J and Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk* 2013; 13(2): 106–111.
46. Ye C, Chen W, Gao Q, et al. Secondary immunodeficiency and hypogammaglobulinemia with IgG levels of <5 g/L in patients with multiple myeloma: a retrospective study between 2012 and 2020 at a university hospital in China. *Med Sci Monit* 2021; 27: e930241.
47. Visentin A, Mauro FR, Rosati S, et al. Protective role immunoglobulin replacement therapy in chronic lymphocytic leukemia: FOCUS on subcutaneous immunoglobulin formulations. *Blood* 2018; 132(Supplement 1): 4954.
48. Legendre P, Chahwan D, Marjanovic Z, et al. Utilization of intravenous or subcutaneous immunoglobulins in secondary immune deficiency (ULTIMATE): A retrospective multicenter study. *Clin Immunol* 2020; 15: 108419.
49. Cinetto F, Neri R, Vianello F, et al. Subcutaneous immunoglobulins replacement therapy in secondary antibody deficiencies: Real life evidence as compared to primary antibody deficiencies. *PLoS ONE* 2021; 16(3): e0247717.
50. De Angelis F, Tosti ME, Capria S, et al. Risk of secondary hypogammaglobulinaemia after rituximab and fludarabine in indolent non-Hodgkin lymphomas: a retrospective cohort study. *Leuk Res* 2015; 39(12): 1382–1388.
51. Dimou M, Iliakis T, Maltezas D, et al. Efficacy-safety of facilitated subcutaneous immunoglobulin in immunodeficiency due to hematological malignancies. a single-center retrospective analysis. *Anticancer Res* 2018; 38(7): 4187–4191.
52. Parikh SA, Leis JF, Chaffee KG, et al. Hypogammaglobulinemia in newly diagnosed chronic lymphocytic leukemia: natural history, clinical correlates, and outcomes. *Cancer* 2015; 121(17): 2883–2891.
53. Van Winkle P, Burchette R, Kim R, et al. Prevalence and safety of intravenous immunoglobulin administration during maintenance chemotherapy in children with acute lymphoblastic leukemia in first complete remission: a health maintenance organization perspective. *Perm J* 2018; 22: 17–141.
54. Derman BA, Schlei Z, Parsad S, et al. Changes in intravenous immunoglobulin usage for hypogammaglobulinemia after implementation of a stewardship program. *JCO Oncol Pract* 2021; 17(3): e445–e453.
55. Svensson T, Höglund M and Cherif H. Clinical significance of serum immunoglobulin G subclass deficiency in patients with chronic lymphocytic leukemia. *Scand J Infect Dis* 2013; 45(7): 537–542.
56. Kano G, Nakatani T, Yagi K, et al. Complicated pathophysiology behind rituximab-induced persistent hypogammaglobulinemia. *Immunol Lett* 2014; 159(1-2): 76–78.
57. Blau IW, Conlon N, Petermann R, et al. Facilitated subcutaneous immunoglobulin administration (fSCIg): a new treatment option for patients with secondary immune deficiencies. *Expert Rev Clin Immunol* 2016; 12(7): 705–711.
58. Jiang F and Verma P. Management of hypogammaglobulinemia and recurrent infections in a chronic lymphocytic leukemia patient receiving ibrutinib. *Ann Allergy Asthma Immunol* 2018; 120(3): 324–325.
59. Wolverton W and McClenathan B. Prolonged hypogammaglobulinemia after adjuvant rituximab for Hodgkin's lymphoma presenting with refractory urticaria. *Ann Allergy Asthma Immunol* 2012; 109(6): 473–474.
60. Reiser M, Borte M, Huscher D, et al. Management of patients with malignancies and secondary immunodeficiencies treated with immunoglobulins in clinical practice: long-term data of the SIGNS study. *Eur J Haematol* 2017; 99(2): 169–177.
61. Duraisingham SS, Buckland MS, Grigoriadou S, et al. Secondary antibody deficiency. *Expert Rev Clin Immunol* 2014; 10(5): 583–591.
62. Günther G and Dreger B. Post-marketing observational study on 5% intravenous immunoglobulin therapy in patients with secondary immunodeficiency and recurrent serious bacterial infections. *Microbiol Immunol* 2013; 57(7): 527–535.
63. Mustafa SS, Jamshed S, Vadamalai K, et al. The use of 20% subcutaneous immunoglobulin replacement therapy in patients with B cell non-Hodgkin lymphoma with humoral immune dysfunction after treatment with rituximab. *Clin Lymphoma Myeloma Leuk* 2020; 20(9): e590–e596.
64. Benbrahim O, Viallard JF, Choquet S, et al. A French observational study describing the use of human polyvalent immunoglobulins in hematological malignancy-associated secondary immunodeficiency. *Eur J Haematol* 2018; 101(1): 48–56.

65. Totadri S, Thipparapu S, Aggarwal R, et al. Imatinib-induced hypogammaglobulinemia in children and adolescents with chronic myeloid leukemia. *Pediatr Hematol Oncol* 2020; 37(6): 539–544.
66. Vacca A, Melaccio A, Sportelli A, et al. Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial. *Clin Immunol* 2018; 191: 110–115.
67. Visentin A, Compagno N, Cinetto F, et al. Clinical profile associated with infections in patients with chronic lymphocytic leukemia. Protective role of immunoglobulin replacement therapy. *Haematologica* 2015; 100(12): e515–8.
68. Burns PB, Rohrich RJ and Chung KC. The levels of evidence and their role in evidence-based medicine: plastic and reconstructive surgery 2011; 128(1): 305–310.