



# Comparison of Diagnostic Criteria for Common Variable Immunodeficiency Disorders (CVID) in the New Zealand CVID Cohort Study

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Accepted: 11 May 2021 / Published online: 8 July 2021

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## Abstract

Common variable immunodeficiency disorders (CVID) are the most frequent symptomatic primary immune deficiencies in adults and children. In addition to recurrent and severe infections, patients with CVID are susceptible to autoimmune and inflammatory complications. The aetiologies of these uncommon conditions are, by definition, unknown. When the causes of complex disorders are uncertain, diagnostic criteria may offer valuable guidance to the management of patients. Over the last two decades, there have been four sets of diagnostic criteria for CVID in use. The original 1999 European Society for Immunodeficiencies and Pan-American Society for Immunodeficiency (ESID/PAGID) criteria are less commonly used than the three newer criteria: Ameratunga et al (Clin Exp Immunol 174:203–211, 2013), ESID (J Allergy Clin Immunol Pract, 2019) and ICON (J Allergy Clin Immunol Pract 4:38–59, 2016) criteria. The primary aim of the present study was to compare the utility of diagnostic criteria in a well-characterised cohort of CVID patients. The New Zealand CVID cohort study (NZCS) commenced in 2006 and currently comprises one hundred and thirteen patients, which represents approximately 70% of all known CVID patients in NZ. Many patients have been on subcutaneous or intravenous (SCIG/IVIG) immunoglobulin treatment for decades. Patients were given a clinical diagnosis of CVID as most were diagnosed before the advent of newer diagnostic criteria. Application of the three commonly used CVID diagnostic criteria to the NZCS showed relative sensitivities as follows: Ameratunga et al (Clin Exp Immunol 174:203–211, 2013), possible and probable CVID, 88.7%; ESID (J Allergy Clin Immunol Pract, 2019), 48.3%; and ICON (J Allergy Clin Immunol Pract 4:38–59, 2016), 47.1%. These differences were mostly due to the low rates of diagnostic vaccination challenges in patients prior to commencing SCIG/IVIG treatment and mirror similar findings in CVID cohorts from Denmark and Finland. Application of the Ameratunga et al (Clin Exp Immunol 174:203–211, 2013) CVID diagnostic criteria to patients on SCIG/IVIG may obviate the need to stop treatment for vaccine studies, to confirm the diagnosis.

**Keywords** CVID · HGUS · NZCS · IVIG · SCIG · Diagnostic criteria

## Introduction

Common variable immunodeficiency disorders (CVID) are the most frequent symptomatic primary immune deficiency in adults and children [1]. Patients with CVID are

susceptible to infective and inflammatory sequelae, mostly as a consequence of late onset antibody failure leading to immune system failure [2].

The causes of CVID are by definition, unknown [3]. All current diagnostic criteria for CVID exclude patients with a definable cause for their immunodeficiency [4–6]. This includes secondary hypogammaglobulinemia as well as causative genetic defects (*NFKB1*, *NFKB2*, *CTLA-4*, *LRBA* etc.). In non-consanguineous populations, approximately 25% of patients with a CVID phenotype have pathogenic mutations, leading mostly to autosomal dominant disorders [7]. In consanguineous societies, the proportion is much greater, largely due to highly penetrant autosomal recessive disorders [8]. If a causative mutation is identified, patients are removed from the broad umbrella diagnosis of CVID and are stated to have a CVID-like

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disorder consequent to a specific genetic defect/inborn error of immunity.

Since the early descriptions of CVID, diagnostic criteria have continued to evolve. In 1999, a joint committee of the European Society for Immunodeficiencies (ESID) and the Pan American Group for Immunodeficiency (PAGID) described diagnostic criteria for CVID [9]. In order to meet the ESID/PAGID (1999) [9] criteria, patients had to be older than 2 years and were required to have significant primary hypogammaglobulinemia, with an IgG 2 standard deviations (sd.) below the mean. Patients were also required to have either an abnormal response to vaccines or absent isohemagglutinins. CVID was a diagnosis of exclusion by the ESID/PAGID (1999) [9] criteria. This definition was deemed relatively simple, allowing the diagnosis to be made in developing countries with limited resources.

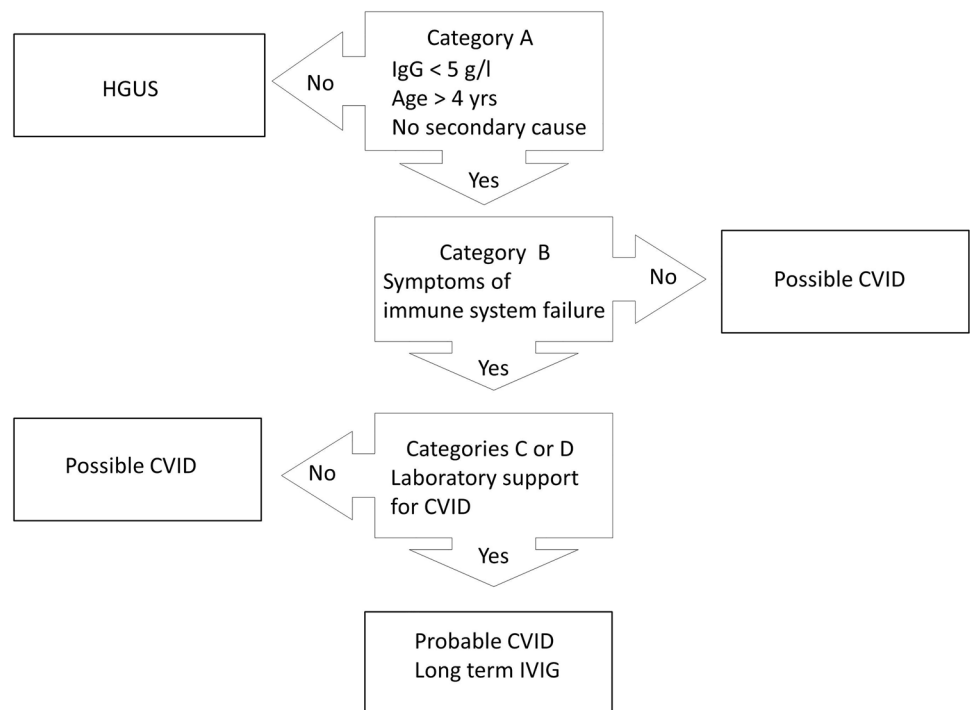
There were practical difficulties with this definition as the precise vaccines and antibody responses were not defined by the ESID/PAGID (1999) [9, 10] criteria. There were at least five criteria for the interpretation of vaccine responses to *S. pneumoniae* [11–13]. Furthermore, many patients had been commenced on IVIG without prior diagnostic vaccination. Because of passively acquired antibodies from subcutaneous or intravenous immunoglobulin (SCIG/IVIG), it was not possible to measure responses to commonly used vaccine antigens such as diphtheria or tetanus toxoid, *H. influenzae* type B (HIB), or *S. pneumoniae*. Stopping SCIG/IVIG for several months to undertake diagnostic vaccine response studies posed an unacceptable risk of severe infections for such patients. Assessing responses to neoantigens such as

the typhoid vaccine are not commonly undertaken in routine clinical practice [14].

Because of these difficulties, new diagnostic criteria for CVID were described in 2013, which could assist with decisions to treat with SCIG/IVIG [4, 15]. The evidence base for these criteria has been previously described in detail, but is summarised here (Fig. 1; supplementary Table 1) [16, 17]. Patients were required to be over 4 years of age and to have a substantial reduction in IgG (< 5 g/l) for which there was no other cause [18]. In the second category, patients had to be symptomatic from their immune system failure. For patients fulfilling the first two criteria, laboratory support either in the form of abnormal blood tests or one of the characteristic histological features of CVID such as granulomas or absence of plasma cells in lymphoid tissues was required [19, 20]. Given the difficulties with assessment, poor vaccine responses were not an absolute requirement for diagnosis. Other characteristic features of CVID including reductions in IgA or IgM, switched memory B cells, poor or short-lived vaccine responses, absent isohemagglutinins, IgG3 deficiency, and genetic variants predisposing to or modifying CVID severity (*TNFRSF13B/TACI*, *TNFRSF13C/BAFFR* etc.) were included in category C of these criteria (supplementary Table 1). These criteria were designed to allow a diagnosis of CVID with greater precision, particularly in patients being treated with SCIG/IVIG.

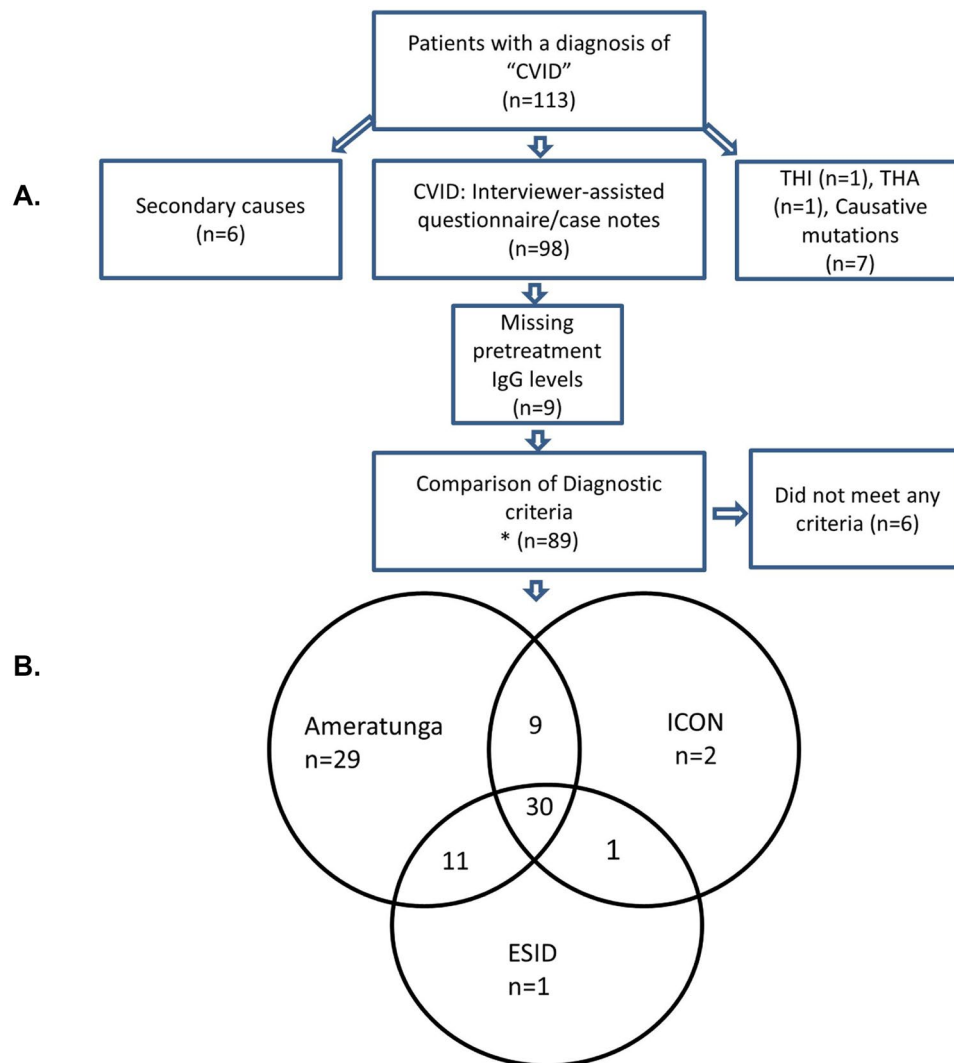
A year later, similar criteria were published by ESID (2014), shown in supplementary Table 2 [5]. Patients were required to have a 2 sd. reduction in IgG and IgA levels as well as some of the well-recognised clinical features

**Fig. 1** Diagnostic algorithm for CVID: Ameratunga et al. (2013) [4]. Patients must meet all major criteria in Category A for consideration of CVID. Category B confirms the presence of symptoms indicating immune system failure (ISF). For probable CVID, patients must also have supportive laboratory evidence of immune system dysfunction (Category C) or characteristic histological lesions of CVID (Category D). Patients with mild hypogammaglobulinemia (IgG > 5 g/l) are termed hypogammaglobulinemia of uncertain significance (HGUS). Symptomatic patients are designated sHGUS; those without symptoms are designated aHGUS. Asymptomatic patients meeting Category A criteria but not other criteria are deemed to have possible CVID.



including granulomatous inflammation and reduction of switched memory B cells. The reduction in IgG was set at 7 g/l rather than 5 g/l in the Ameratunga et al. (2013) [4] criteria. Poor vaccine responses were not mandatory for the diagnosis and could be replaced by a reduction in memory B cells or absent isoheamagglutinins. Like the Ameratunga et al. (2013) [4] criteria, this could potentially allow a diagnosis of CVID in patients on SCIG/IVIG.

In 2016, a group of clinical Immunologists formulated the International Consensus Criteria (ICON) for CVID (supplementary Table 3) [6]. These were similar to the original ESID/PAGID (1999) [9] criteria in that poor vaccine responses were a requirement for the diagnosis, providing the patient had an IgG level > 1 g/l. A single abnormal vaccine response was deemed sufficient to establish the diagnosis of CVID in a patient with primary hypogammaglobulinemia. In contrast to the ESID (2014) criteria, the ICON (2016) [6] criteria allowed



**Fig. 2** **A** STARD (Standards for Reporting of Diagnostic Accuracy) diagram of the current analysis of the NZCS. Patients were excluded if they had either a secondary cause for their hypogammaglobulinemia or if they had a causative mutation. \*Seventy-nine of the eighty-nine patients (88.7%) received their diagnosis of CVID before 2013. In nine patients, the pre-treatment IgG levels could not be ascertained from clinical notes. Because the three sets of diagnostic criteria could not be applied to these patients, they were removed from further analysis. **B** Application of the three sets of diagnostic criteria (names abbreviated in the diagram) in the NZCS to eighty-nine patients for whom pre-treatment IgG levels were available. The relative sensi-

activities for the CVID diagnostic criteria were as follows: Ameratunga et al. (2013) [4] possible and probable CVID, 88.7%; ESID (2014), 48.3%; and ICON (2016) [6] criteria, 47.1%. Six patients had HGUS by the Ameratunga et al. (2013) [4] criteria and did not meet the ICON (2016) [6] or ESID (2014) criteria. Two patients with HGUS by the Ameratunga et al. (2013) [4] criteria met the ICON (2016) [6] and one met ESID (2014) criteria for CVID. One patient with HGUS met both ESID (2014) and ICON (2016) [6] criteria. THA transient hypogammaglobulinemia of adulthood, TH1 transient hypogammaglobulinemia of infancy

a reduction of either IgA or IgM in addition to a 2 sd. reduction in IgG. Both the ESID (2014) and ICON (2016) [6] criteria excluded patients with late onset combined immunodeficiency (LOCID), although it has been suggested LOCID should remain within the broad overlapping phenotypes of CVID and CVID-like disorders [21].

The primary aim of this analysis was to compare current diagnostic criteria in a well-characterised cohort of patients with CVID. The New Zealand (NZ) CVID study (NZCS) commenced in 2006 [22]. This long-term prospective study sought to improve the understanding of this group of disorders in NZ. Since the majority of patients in the NZCS commenced SCIG/IVIG treatment before the advent of the newer diagnostic criteria for CVID, this is a relatively unbiased cohort to assess the performance of these criteria.

## Methods

Patients with a diagnosis of CVID in NZ were invited to join the study. NZ (pop 5 M) is a sparsely populated developed country, where most of the population reside in urban centres. Auckland, Wellington and Christchurch offer adult clinical immunology services. All clinical immunologists in NZ were contacted in 2006 and encouraged to enrol their patients in this study. One internist from each of the regional public hospitals around NZ was also contacted and encouraged to enrol patients in the study. This nation-wide research project was approved by the multiregional ethics committee of the New Zealand Ministry of Health (MEC 06/10/134) and the Auckland District Health Board (ADHB) ethics committee (3435).

The Standards for Reporting of Diagnostic Accuracy (STARD) criteria for the present analysis were as follows: Adult (> 16 years) patients were eligible if their pre-treatment IgG levels were available. Those with either a causative mutation or secondary causes for their hypogammaglobulinemia were excluded. Given the long follow-up, most patients with secondary causes such as malignancy would have been identified in the NZCS.

Each citizen or permanent resident in NZ is assigned a unique National Health Index (NHI) number. Computerised clinical records from regional public hospitals are linked to the NHI. Long-term prospective studies utilising the NHI therefore have a very high follow up rate in NZ, apart from patients emigrating to other countries.

Following informed consent, clinical information was obtained by an interviewer-assisted questionnaire and electronic notes were reviewed to obtain computerised laboratory data. Laboratory tests are performed solely by New Zealand Government (NZG)-funded public and private laboratories, and the results are electronically linked to the NHI. In addition to the prospective data, there was also a

retrospective element in that NHI-linked laboratory data dating back to when the patient first made contact with the health system was extracted. The methodology used in the NZCS is identical to the NZ hypogammaglobulinemia study (NZHS) [23]. The NZHS described the natural history of hypogammaglobulinemia, where patients were not placed on SCIG/IVIG for at least 6 months. Of the one-hundred and twenty-one patients in the NZHS, seventeen were subsequently diagnosed as having CVID and are included in this analysis.

NZ has a socialised health system where SCIG/IVIG is funded by the NZG and is dispensed exclusively by the NZ

**Table 1** Laboratory results from patients included in the study. Not all patients had diagnostic vaccine challenge responses undertaken prior to commencing SCIG/IVIG. Pre-treatment and post-treatment antibody levels are shown. Prior to the consensus approach to diagnostic vaccinations, there was variability in which vaccines were administered [25]. \*IgG levels are not normally distributed [42]. \*\*The higher antibody thresholds in the Ameratunga et al. (2013) [4] criteria are based on studies of normal individuals in the community [4]. The ESID (2014) and ICON (2016) [6] criteria have set the antibody response thresholds at protective levels for diphtheria (Dip), tetanus (Tet), and *H. influenzae* (HIB) vaccines

Laboratory results	n = 89
IgG (g/l) mean	2.98 (n = 89)
Nr 7–14 g/l	CI (2.66–3.3)
	Range 0.1–6.1 g/l
	*Median 3.0 g/l
	25 <sup>th</sup> /75 <sup>th</sup> percentiles
	1.75–4.29 g/l
IgA (g/l) < 0.7 / < 0.07 g/l	75/45 (n = 88)
Nr 0.7–3.0 g/l	Normal IgA (n = 9)
Missing data	(n = 1)
IgM (g/l) < 0.4	65/86
Nr 0.4–2.5 g/l	n = 3
Missing data	
Absent B cells	4/72
Reduced switched memory B cells (CD19+, CD27+, IgD–)	41/71
Vaccine challenge responses	Individuals reaching threshold/tested
Pre Dip > 0.1 IU/ml	16/48
Pre Dip > 1 IU /ml	0/48
Post Dip vac × 4	5/39
**Post Dip vac > 1 IU/ml	4/43
Pre Tet > 0.1 IU/ml	29/53
Pre Tet > 1 IU/ml	2/54
Post Tet vac × 4	9/45
**Post Tet vac > 1 IU/ml	30/47
Pre HIB > 0.15 µg/ml	22/37
Pre HIB > 1 µg/ml	8/37
Post HIB vac × 4	8/26
**Post HIB vac > 1 µg/ml	24/32
Post Pneumovax®	21/32
Binding site > 16	4/29
Serotypes > 17/23	
Isohemagglutinins > 1:2	17/20

Blood Service (NZBS). A recent audit by the NZBS has shown the NZCS comprises approximately 70% of patients known to be on SCIG/IVIG treatment for CVID in NZ [24].

The decision to treat with SCIG/IVIG is by consensus in Auckland where most of the patients were domiciled. Requirements for SCIG/IVIG included diagnostic vaccine challenge responses to HIB, Pneumovax® as well as diphtheria and tetanus toxoids, in patients with an IgG > 3 g/l [25]. In cases of profound primary hypogammaglobulinemia (IgG < 3 g/l), diagnostic vaccine responses are not prerequisites for SCIG/IVIG treatment. Over the last decade, such a clinical approach to treatment has ensured greater consistency in the workup of patients with hypogammaglobulinemia.

For tetanus toxoid, diphtheria toxoid, and HIB vaccine responses, antibody thresholds have been set at protective levels or a fourfold increase in titre by the ESID (2014) and ICON (2016) [6] criteria. In the Ameratunga et al. (2013) [4] criteria, patients were required to reach a higher antibody level, based on the response of normal individuals in the community [4]. While controversial [13], the American Academy of Allergy, Asthma and Immunology (AAAAI) recommendation of a 70% increase in individual pneumococcal serotypes to levels > 1.3 µg/ml following Pneumovax® vaccination was adopted [26]. Alternatively, patients were required to reach 16 U in the Binding Site® assay, which is stated to confer a response against *S. pneumoniae* [27, 28]. Diagnostic genetic testing is increasingly being undertaken as part of the initial work up of newly identified patients [29]. It is being gradually implemented in patients with long-standing diagnoses of CVID.

Patients were assessed in late 2020 to determine if they met one or more of the three newer sets of diagnostic criteria (supplementary Tables 1–3). Deceased patients were included in the analysis.

## Results

One hundred and thirteen patients were enrolled in the NZCS (Fig. 2A). Thirteen patients died during the course of the study. Nine of the living patients in this cohort were not on SCIG/IVIG. This includes three asymptomatic patients described in the NZHS, with profound hypogammaglobulinemia (IgG < 3 g/l), who declined SCIG/IVIG and have remained well for over a decade [23].

Patients with a variety of secondary causes were excluded (Fig. 2A). These included adverse reactions to drugs and enteropathy [30–33]. Of the one hundred and thirteen patients, seven of seventeen patients tested had causative genetic defects and were excluded from further analysis. This included a brother and sister where *NFKB1* mutations (c.465dupA) were first shown to be a common

cause of CVID-like disorders (Fig. 2A) [21, 34, 35]. The deceased sister with *NFKB1* haploinsufficiency had LOCID as defined by the ESID (2014) criteria [21]. A *NFKB1* (c.357\_358del) mutation was recently identified in another patient. One deceased patient with LOCID was presumed to have had a gain of function mutation of *STAT3* (c.2147C>T) which was subsequently identified in her two sons, while one patient had haploinsufficiency of *CTLA4* (c.412C>T). Another family had an epistatic interaction between TACI (C104R) and *TCF3* (T168fsX191) mutations leading to a severe CVID-like disorder [36, 37]. The asymptomatic uncle was homozygous for the TACI (C104R) mutation [38]. Patients with mutations predisposing to or modifying disease severity (*TNFRSF13B/TACI*, *TNFRSF13C/BAFFR* etc.) were retained in the analysis [39, 40].

One adult patient had transient hypogammaglobulinemia of infancy (THI) and was able to discontinue IVIG treatment [41]. Another patient had transient hypogammaglobulinemia of adulthood (THA) and was also able to discontinue IVIG treatment [23]. Because there was an alternative explanation for the hypogammaglobulinemia, both were excluded from this analysis.

Forty-six patients had possible CVID, and thirty-three had probable CVID (88.7% of total; Figs. 1, 2B) by the Ameratunga et al. (2013) [4] criteria. Ten had hypogammaglobulinemia of uncertain significance (HGUS) as they had IgG levels between 5 and 6.9 g/l (Fig. 1). Two with HGUS met the ICON (2016) [6] and another met the ESID (2014) criteria for CVID (Fig. 2B). Another HGUS patient met both ESID (2014) and ICON (2016) [6] criteria. Six with HGUS did not meet either the ESID (2014) or ICON (2016) [6] criteria (Fig. 2A).

There was agreement between all three criteria in thirty (33.7%) patients (Fig. 2B). These patients had undergone diagnostic vaccine challenges and were shown to have impaired responses to at least one vaccine. Nine patients were excluded by the ESID (2014) criteria as they had normal IgA levels; and the IgA level was missing in one. Forty-three (48.3%) patients met the ESID (2014), and forty-two (47.1%) met the ICON (2016) [6] criteria for CVID.

## Discussion

By definition, the causes of CVID are unknown and there is no single clinical feature or laboratory test that is pathognomonic for the disorder. When there is no gold standard for the diagnosis and the cause of a disorder is not known, diagnostic criteria play an important role in identifying cases and assisting with their management [15]. In the case of CVID, diagnostic criteria play a critical role in determining eligibility for SCIG/IVIG treatment [15]. In this analysis, the relative sensitivity of the three newer sets of diagnostic criteria for CVID was compared in the NZCS. Because the majority

(88.7%) of patients were diagnosed before 2013, application of the three newer sets of criteria to this cohort reduces the risk of fallacious circular logic. The low numbers of patients diagnosed after 2013 precluded statistical comparisons with diagnoses made before this date. The first recommendation from this study is that CVID diagnostic criteria should be applied retrospectively to reduce the risk of bias.

All CVID diagnostic criteria exclude patients with a known cause for their hypogammaglobulinemia [39]. This includes secondary causes as well as causative mutations such as *NFKB1* and *TCF3* [43]. Patients with a causative mutation were removed from the present analysis but those with mutations predisposing to or modifying disease severity (*TNFRSF13B/TACI*, *TNFRSF13C/BAFFR* etc.) were retained [44]. The prevalence of these variants far exceeds that of CVID. All patients with CVID should be offered genetic testing [45]. At this time, seventeen patients have undergone genetic testing in this cohort. It is likely causative genetic defects will be identified in some of the remaining NZCS patients, who will then be removed from the umbrella diagnosis of CVID. The second recommendation of this study is that diagnostic genetic studies should be undertaken in all patients with a CVID phenotype.

We could not ascertain pre-treatment IgG levels in nine patients (Fig. 2A). Public hospitals began converting paper-based case notes to linked electronic files 15 years ago in NZ. Some patients have been on immunoglobulin replacement for over three decades. Missing data is common in long-term studies, as seen below in the Danish CVID cohort. [46].

Differences between CVID diagnostic criteria have been previously discussed [1, 17, 39]. As noted above, the original ESID/PAGID (1999) [9] criteria proved difficult to use in clinical practice. Subsequent to the publication of the ESID/PAGID (1999) [9] criteria, there have been major advances in the understanding of CVID. The three more recent criteria have allowed CVID to be diagnosed with greater precision (supplementary Tables 1–3) [4–6]. The Ameratunga et al. (2013) [4] and ESID (2014) criteria include newly discovered characteristic features of CVID such as reduced switched memory B cells [47]; acknowledging these may need to be repeated [48].

As seen in this study, each of the three newer sets of diagnostic criteria has advantages and limitations. In the present study, seventy-nine of eighty-nine (88.7%) met the Ameratunga et al. (2013) [4] criteria for possible or probable CVID, where pre-treatment IgG levels were available. The Ameratunga et al. (2013) [4] criteria have set a threshold of 5 g/l compared to 7 g/l for the ESID and ICON criteria. Ten hypogammaglobulinemic patients with an IgG > 5 g/l were deemed to have HGUS and were excluded from the Ameratunga et al. (2013) [4] criteria. Two HGUS patients met the ICON (2016) [6] criteria and another, the ESID (2014) criteria for CVID (Fig. 2B). Another HGUS patient met both the ESID (2014)

and ICON (2016) [6] criteria. It is apparent from this study that some patients with symptomatic primary hypogammaglobulinemia may not receive a diagnosis of possible or probable CVID by the Ameratunga et al. (2013) [4] criteria, which could adversely impact their eligibility for SCIG/IVIG treatment. Conversely, the NZHS has shown that up to 41.6% of adult patients with symptomatic hypogammaglobulinemia (sHGUS), including those with bronchiectasis, can normalise their IgG [23]. This phenomenon has been termed THA. THA was much less likely in patients with IgG levels of 5 g/l or less in the NZHS. Having a lower threshold for IgG may improve the specificity of the diagnosis at the expense of sensitivity.

The ESID (2014) criteria require a reduction of IgA, while the ICON (2016) [6] criteria accept a reduction of either IgA or IgM. The Ameratunga et al. (2013) [4] criteria do not require a reduction in IgA or IgM. Nine patients had normal IgA levels in this cohort and did not meet the ESID (2014) criteria for CVID. The mandatory requirement for reduced IgA levels may disadvantage patients with a reduction only in IgG and IgM and is the reason for reduced sensitivity of these criteria. Such patients would receive a diagnosis of CVID by the ICON (2016) [6] and Ameratunga et al. (2013) [4] criteria.

Diagnostic vaccine challenge responses are required for the ICON (2016) [6] criteria unless the patient has profound hypogammaglobulinemia (IgG < 1 g/l; supplementary Table 3). Patients commencing IVIG prior to the year 2000 rarely had diagnostic vaccine responses undertaken in NZ. Furthermore, patients with IgG levels < 3 g/l are not currently required to have diagnostic vaccine challenges in Auckland prior to commencing SCIG/IVIG [25]. This is the primary reason why the ICON (2016) [6] criteria had relatively low sensitivity (47.1%) in the NZCS.

In contrast, diagnostic vaccine challenges are not mandatory in the ESID (2014) CVID diagnostic criteria, providing the patient has a reduction in switched memory B cells or absent isohemagglutinins (supplementary Table 2). The ESID (2014) criteria identified forty-three (48.3%) patients in the NZCS as having probable CVID.

Difficulties with interpreting diagnostic vaccine challenge responses were discussed in the NZHS [23]. The NZCS, like the NZHS has shown there, is a hierarchy of vaccine responses in patients with severe primary hypogammaglobulinemia (Table 1). Tetanus toxoid and HIB elicit robust antibody responses, while diphtheria and Pneumovax® generate lower titres following vaccination. Given this is a study of adults, patients in the NZCS (and NZHS) have received their primary immunisation series in childhood. Memory B cell responses from childhood vaccinations are likely to have contributed to higher anamnestic humoral responses to the vaccine challenges (Table 1). The NZCS demonstrates patients with symptomatic primary hypogammaglobulinemia should not be denied SCIG/IVIG on the basis of excellent responses to tetanus toxoid or HIB. This is the third recommendation of this study.

The NZHS has previously shown that symptomatic state is a better predictor of immune system failure in hypogammaglobulinemia than vaccine responses [23]. Regardless of vaccine responses, many more symptomatic patients with hypogammaglobulinemia (sHGUS) progressed to SCIG/IVIG treatment compared to those who were clinically well (aHGUS) in the NZHS.

There are differences in whether symptoms are required for a diagnosis of CVID. The Ameratunga et al criteria require symptoms attributable to the immune system failure for a diagnosis of probable CVID. The ESID (2014) criteria allow a diagnosis of CVID in an asymptomatic patient if there is a family history of a PID (supplementary Table 2). The ICON (2016) [6] criteria similarly allow asymptomatic patients to be diagnosed if they meet criteria 2–5 (Supplementary Table 3).

Apart from the NZHS, two international studies have compared these criteria in the same cohort of CVID patients. Selenius et al. compared the performance of the ESID/PAGID (1999) [9], the Ameratunga et al. (2013) [4] and the ICON (2016) [6] criteria in their CVID cohort from Finland [49]. The ESID/PAGID (1999) [9] and the Ameratunga et al. (2013) [4] criteria appeared to have identified the same group of patients. The ICON (2016) [6] criteria identified fewer patients, mainly because most were on long term SCIG/IVIG. Like the NZCS, most of these Finnish patients had not undergone diagnostic vaccine studies before commencing SCIG/IVIG. Selenius et al. did not feel the revised ESID registry (2014) criteria could be applied because of the mandatory requirement for reduced IgA levels for the diagnosis.

In another Nordic study, all CVID patients were identified in Denmark from a national registry [46]. Of the one hundred and seventy-nine with CVID, 95% were on SCIG/IVIG. This study showed twenty-four patients (13.4%) had probable and one-hundred and six (59.2%) had possible CVID by the Ameratunga et al. (2013) [4] criteria. Like the NZCS, most Danish patients did not have diagnostic vaccine challenge studies prior to SCIG/IVIG replacement. Forty-nine (27.4%) patients in the Danish study were stated to have ‘inadequate investigation’, similar to the nine patients in the NZCS, who did not have pre-treatment IgG levels. Adjusting for these NZCS patients, the relative sensitivity of the Ameratunga et al. (2013) [4] criteria would decrease from 88.7 to 80.8%, which is similar (72.6%) in the Danish study.

The Danish study also applied the PAGID/ESID (1999) [9] criteria, but not the revised ESID (2014) registry or ICON (2016) [6] criteria. According to the ESID/PAGID (1999) [9] criteria, fifty (27.9%) patients were categorised as ‘probable CVID’, six (3.4%) patients were categorised as ‘possible CVID’ by the ESID/PAGID (1999) [9] criteria, while one-hundred and twenty three (68.7%) patients were unclassified because of insufficient data.

Like the Finnish and Danish studies, the NZCS has shown the Ameratunga et al. (2013) [4] criteria identify most patients as having possible or probable CVID where the majority are being treated with SCIG/IVIG. If a retrospective diagnosis of CVID is required by third party payers, application of the Ameratunga et al. (2013) [4] criteria may obviate the need to stop SCIG/IVIG treatment to determine vaccine responses. This may reduce the risk of severe infections, while diagnostic vaccine challenges are being undertaken.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12016-021-08860-7>.

**Acknowledgements** This nation-wide study was approved by the multi-regional ethics committee of the New Zealand Ministry of Health (MEC 06/10/134) and the Auckland District Health Board (ADHB) ethics committee (3435). Informed consent was required for this study. Consent to publish was part of the ethics approval and patient consent. RA conducted the study, S-TW checked the data, and HL and RS made editorial contributions to the manuscript. We thank our patients for participating in these studies for the benefit of others. We thank colleagues for referring patients to our studies. The original publications relevant to diagnostic criteria and NZ patients described in case reports are cited in this article. No data will be made available as it could identify individual patients.

**Funding** The authors received financial support from ASCIA, the A+ Trust, and IDFNZ.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

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