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Perspective

Dearth of ICD Codes for Complications of Immune Checkpoint Inhibitors Impedes Clinical Care and Research

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Abstract

Immune checkpoint inhibitors (ICIs) are a rapidly expanding class of targeted therapies effective in the treatment of various cancers. However, while efficacious, ICIs have been associated with treatment complications, namely immune-related adverse events (irAEs). IrAEs of the endocrine system are among the most commonly reported irAEs, but despite their high incidence, standardized disease definitions and endocrine IrAE-specific International Classification of Diseases (ICD) codes remain lacking. This dearth of standardized nomenclature and ICD codes has in many ways impeded both the clinical care of patients and the progress of endocrine irAE-related research. ICD codes are used internationally and are essential for medical claims reporting in the health care setting, and they provide a universal language system for recording, reporting, and monitoring diseases. These codes are also a well-accepted form of electronic health record data capture that facilitates the collection, storage, and sharing of data. Therefore, the lack of standardized disease definitions and ICD codes has been associated with misclassification and suboptimal management of individuals with endocrine irAEs and has also been associated with reduced data availability, comparability, and quality. Harmonized and clinically relevant disease definitions along with the subsequent development of endocrine-irAE-specific ICD codes will provide a systematic approach to understanding the spectrum and burden of endocrine irAE diseases, and will have a positive effect across clinical, public health, and research settings.

Key Words: immune checkpoint inhibitors, endocrine immune-related adverse effects, immunotherapy, international classification of disease, nomenclature

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EHR, electronic health record; ICD, International Classification of Diseases; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; WHO, World Health Organization.

Immune checkpoint inhibitors (ICIs) are a class of targeted therapies proven to be effective in improving cancer outcomes in a variety of clinical settings [1]. These agents are monoclonal antibodies that block specific immune checkpoints—receptors present on the surface of T lymphocytes that are essential for the maintenance of immune homeostasis, self-tolerance, and the modulation of the physiological immune response [1].

Given its mechanism of action, ICI therapy has been associated with altered immunologic tolerance and a higher risk of developing an immune response directed at autoantigens [1]. These reactions have been termed *immune-related adverse events* (irAEs). IrAEs can involve any organ system, but the most reported toxicities include those of the skin, pulmonary, gastrointestinal, and endocrine systems [1]. Common endocrine irAEs include thyroiditis and hypophysitis, while rarer endocrine irAEs include adrenalitis, diabetes mellitus, hypoparathyroidism, and hypogonadism [1].

Although life-threatening endocrine irAEs are rare, clinical presentations of endocrine irAEs are often diverse and may mimic more common endocrine and nonendocrine conditions, including nonspecific side effects of cancer therapies. This can lead to misdiagnosis and significant detrimental consequences in the management of patients, such as inappropriate or delayed treatment. Therefore, early and correct identification and classification of endocrine irAEs are essential for optimal patient care.

Defining Endocrine Immune-related Adverse Events in Clinical Practice

To date, there is a lack of standardized diagnostic criteria and classification codes to assist clinicians with the identification and management of endocrine irAEs. The World Health Organization (WHO) maintains and publishes the International Classification of Diseases (ICDs), which is used globally for clinical documentation of morbidity, causes of mortality, decision-making in health care management, health care reimbursement, public health, and epidemiology research. ICD codes are regularly revised to ensure that advances in medicine

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and our understanding of diseases are reflected in the coding system. The latest version of the code is the ICD-11, which went into effect in January 2022 [2].

Different countries use adaptations of the ICD codes based on the needs of their populations and health systems. Reviewing, modifying, and implementing changes to the ICD codes means that the timeline from WHO ICD revision releases to adoption in individual countries are variable. In the United States, for example, the ICD-clinical modification (ICD-CM) codes are adapted from the WHO ICD codes by the National Center for Health Statistics (NCHS) and the Centers for Medicare and Medicaid Services. The ICD-10 went into effect internationally in 1994; however, the ICD-10-CM was not adopted in the United States until 2015. Similarly, there is an Australian modification (ICD-AM) used in Australia and New Zealand, and a Canadian modification (ICD-CA) of the ICD codes. As of January 2023, the United States, Australia, New Zealand, and Canada continue to use their adapted versions of the ICD-10.

The greatest and most valuable difference between the ICD-11 and earlier revisions is the addition of a fully digital and web-based design, which aims to reduce certain barriers and broaden the global reach of the ICD system. The online versions are available in a variety of languages and is accessible anywhere with web access [2]. However, despite these improvements, the ICD-11, like the previous version, provides codes only for common non–ICI-induced endocrine conditions, and codes in the setting of ICIs remain lacking. This is problematic as the evaluation and management of endocrine conditions when they manifest as irAEs may differ from when they exist as primary conditions, and therefore a clear distinction in reporting nomenclature is essential.

As an illustration, ICI-related thyroiditis is the most common endocrine irAE and tends to evolve rapidly. A patient may initially present with either thyrotoxicosis or hypothyroidism, which can be followed by euthyroidism or permanent hypothyroidism. Thyroid autoantibodies may be present in approximately two-thirds of patients who develop permanent hypothyroidism. It is important to recognize that in the typical hyperthyroid phase of ICI-induced thyroiditis, antithyroid medications are not indicated. Additionally, in contrast to the clinical course for Hashimoto hypothyroidism, which is usually slowly progressive, leading to permanent hypothyroidism and a need for thyroid hormone replacement, for ICI-related thyroid dysfunction, the evolution is rapid and thyroid hormone replacement is considered only if recovery does not occur. Using the ICD-11, a clinician could choose any number of diagnosis codes to classify an individual with ICI-induced thyroid dysfunction, including "acute thyroiditis," "painless thyroiditis," "thyroiditis, unspecified," "thyrotoxicosis, unspecified," "hypothyroidism due to medicaments or other exogenous substances," "hypothyroidism, unspecified," and "disorders of the thyroid gland or thyroid hormones system, unspecified." This nonspecific classification, or potential mislabeling of endocrine irAEs, has diagnostic, clinical, and research implications. By creating and applying endocrine irAE-specific ICD codes, clinicians will be able to document more accurately the causal relationship between ICIs and endocrine-irAEs, and will be able to develop appropriate management plans by immediately being cognizant that ICI therapy is the underlying cause for the development of the endocrine condition. Additionally, understanding risk factors for developing thyroid dysfunction with ICIs, factors associated with recovery, and associations with hospitalization, other irAEs, and mortality is difficult without specific ICD codes.

Several specialty working groups and societies have recognized the issues associated with the lack of standardized terminology for endocrine irAEs and have attempted to overcome this obstacle by developing diagnostic and management guidelines [3, 4]. However, navigating the inconsistencies and discrepancies between the various guidelines remains a challenge.

The Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted as the standard classification and severity grading scale for AEs associated with cancer therapies. However, it is important to recognize that this grading system was designed primarily for use in the clinical trial and oncological settings. Therefore, while a number of guidelines rely predominantly on the latest CTCAE (version 5) [5] to define and report endocrine irAEs [3, 4], several limitations exist when using this system. First, many clinical subspecialists who manage irAEs may not be familiar with this grading system and therefore may not refer to it when classifying endocrine irAEs. Second, the CTCAE does not always correlate with standard clinical practice and its incorporation into everyday care may be challenging and counterintuitive for clinicians. For example, the CTCAE defines immune-related thyroid dysfunction as either hyperthyroidism or hypothyroidism. However, this is generally not how abnormal thyroid laboratory results are thought of in clinical practice, as clinicians often consider the underlying etiology. For example, hyperthyroidism from thyroiditis (as usually seen with ICIs) is very different from hyperthyroidism from Graves disease. However, these conditions cannot be distinguished with the CTCAE. Oversimplifying definitions of endocrine irAEs can therefore lead to disease misclassification and mismanagement. Similarly, while endocrinologists often suspect checkpoint inhibitor–associated diabetes in individuals with clinical evidence of rapid-onset hyperglycemia, swift progression to insulin deficiency, and diabetic ketoacidosis, the CTCAE defines "hyperglycemia" rather than the clinical characteristics or the underlying pathophysiology of the diabetes [5]. This limits the utility of the CTCAE in assisting clinicians with the diagnosis and, more important, the differentiation of checkpoint inhibitor–associated diabetes from other forms of diabetes. Another limitation of the CTACE is that it does not always correlate with disease severity. For example, the CTCAE (version 5) definition for grade 3 hyperglycemia is "insulin therapy initiated; hospitalization indicated," [5] whereas from an endocrinologist's perspective, initiation of insulin does not always equate to a hospital admission.

Therefore, the development of disease-specific ICD codes will facilitate and act as an adjunct to the CTCAE in standardizing the diagnostic classification and reporting of endocrine irAEs. In addition, the universal acceptance of ICD codes will enable providers and payers to systematically track and compare information about patients' endocrine irAEs or treatments, and thus potentially regulate and improve clinical care and provider performance.

Defining Endocrine Immune-related Adverse Events in the Research Setting

Beyond the effect on clinical practice, the heterogeneity of endocrine irAE definitions has also impeded the progress and quality of epidemiological and outcomes research.

Because of the considerable heterogeneity in the way studies currently define and obtain their endocrine irAE populations, the comparability and interpretability of these existing studies are somewhat limited. In addition, inconsistencies in the definitions and therefore the documentation of endocrine irAEs make the tracking of the disease, the chronic burden of endocrine conditions caused by cancer treatments, and costs challenging from a public health and health service perspective.

The underlying source of the heterogeneity is likely multifactorial. However, a major contributor is likely due to the lack of endocrine irAE-specific ICD codes [6]. Electronic health records (EHRs) contain an abundance of health data that are often inexpensive, easily accessible, and can be collected without interfering with the delivery of care. ICD codes have become a commonly accepted method of EHR data capture that facilitates the collection, storage, and sharing of data. The specificity of ICD codes makes them a valuable method of determining health status and risk factors in defined populations, as well as measuring the safety and efficacy of patient care. In addition, ICD codes provide a systematic approach to reporting medical claims data, and therefore enables health care services to track and monitor disease-specific costs.

However, in the absence of disease-specific codes, treating clinicians are left with the options of either entering a nonspecific code or omitting the event completely from the EHR. Therefore, currently available ICD codes are often an imprecise and unreliable data capture method when attempting to identify the entirety of endocrine irAE populations, or endocrine irAE-related medical claims. A recent study demonstrated that the ability of nonspecific ICD codes to identify true irAEs was inferior when compared to manual chart review, and that 46% of true irAEs would have been missed if nonspecific ICD codes were relied on alone without subsequent manual review [6]. As a consequence, investigators who heavily rely on claims and ICD code–based EHR data curation often need to further "clean" the data, which can be costly and resource intensive. Furthermore, manual review of "free text" is still subject to complexities and challenges. Without a consensus on endocrine irAEs diagnostic definitions, variability will inevitably exist in the documentation of endocrine irAEs by clinicians. Also, the interpretation of medical notes and laboratory results is ultimately at the discretion of the retrospective reviewer, thus potentially introducing bias and additional variability. Establishing endocrine irAE-specific ICD codes is therefore a logical and achievable next step in improving data availability, quality, and accuracy.

Future Directions

Neurology and dermatology irAE working groups have recognized the multiple benefits associated with standardization, and have subsequently published consensus definitions for various organ-specific irAEs based on the Delphi panel method [7, 8]. This is a validated method often used to coordinate consensus from subspecialty experts based on "real-world" clinical experience in the absence of definitive evidence [7, 8].

Conclusions

Evidence-based and clinically relevant diagnostic and severity definitions of endocrine irAEs are needed. These disease definitions, along with the subsequent development of endocrine irAE-specific ICD codes, will provide a systematic approach to documenting the spectrum of endocrine irAE diseases. While the primary goal for standardization of endocrine irAE definitions and ICD codes is to provide increased accuracy and diagnostic specificity for our patients, these changes will most definitely have additional positive effects across clinical, public health, and research settings.

Disclosures

Y.M.M.C. and O.P.R.H. report no disclosures. A.S. reports speaker activities for Merck and consulting for Bristol Myers Squibb. E.J.G. reports consulting for Novartis Pharmaceuticals, Seagen, and Flare Therapeutics.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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