Editorial

Classification in Systemic Sclerosis

Accurate classification of systemic sclerosis (SSc) has been an evolving issue in both pediatric and adult rheumatology literature. The need for classification criteria has been long recognized as a necessity for scientific inquiry, as SSc is a heterogeneous disease with variable expression, and prognosis is dependent on disease severity and target organ involvement. The utilization of classification criteria in research allows comparison of study findings in similar patient subgroups across observational studies and clinical trials.

Scleroderma of childhood has traditionally been classified as juvenile localized scleroderma (JLS) and juvenile systemic sclerosis (JSSc). JLS is further classified by morphea (both localized and generalized) and linear scleroderma, including *en coup de sabre* lesion of the forehead and Parry-Romberg hemifacial atrophy. Peterson, *et al* have proposed an alternative classification for morphea[1]. In either case, it has been believed that JLS is a benign, self-limited condition with manifestations confined to the skin and/or subcutaneous tissues[2]. However, a recent multinational observational study of 750 patients with JLS reported that 22.4% (168 patients) presented with one or more extracutaneous manifestations. Arthritis and neurologic changes were not necessarily confined to the side of skin involvement, suggesting a systemic autoimmune condition[3]. Zulian, *et al* have proposed that within the classification of childhood scleroderma lies a third class, "JLS with extracutaneous manifestations."

The lack of universally accepted classification criteria for JSSc has resulted in a multinational effort to develop criteria through consensus methods. Three definitions for preliminary classification criteria were presented at the 2005 American College of Rheumatology (ACR) meeting[4]. These included (1) presence of skin sclerosis/induration and at least 2 minor criteria; (2) Raynaud's phenomenon and skin sclerosis/induration and at least one minor criterion; (3) Raynaud's phenomenon and skin sclerosis/induration and at least 2 minor criteria. Future investigators will need to evaluate the validity and reliability of these criteria before they can be confidently used in clinical trials involving patients with JSSc.

Similarly, the concept of classification criteria for SSc of adulthood has been evolving. Although a number of classification systems have been proposed[5-7], the most widely cited criteria are the 1980 Preliminary Criteria for the Classification of Systemic Sclerosis[8]. Initially created to be specific rather than sensitive to minimize false-positive diagnosis, the current utility of these criteria has been questioned, including criticism for excluding patients who have been classified as having SSc by experienced clinicians, in particular those with the limited subtype of disease[9]. The addition of Raynaud's phenomenon and nailfold capillary microscopy and SSc selective antibodies as additional minor criteria has been shown to improve the sensitivity of these criteria from 33.4 to 91.5%[9]. Some investigators have suggested a separate classification for SSc *sine* scleroderma[6]; however, Poormoghim, *et al* found no significant difference in disease manifestations, prognosis, and survival in this subgroup compared to patients with limited SSc[10].

Undoubtedly, as our understanding of SSc improves, the criteria by which we classify patients will also become more refined. Due to the importance of this endeavor, the ACR is currently developing standards to which future iterations of this process should be held. The ACR Subcommittee on Classification and Response Criteria of the ACR Quality Measures Committee has proposed methods for developing and validating such criteria, and discusses the role of the ACR with respect to these endeavors[11].

In this issue of *The Journal*, Scalapino, *et al* compare clinical characteristics, laboratory data, and survival between patients with childhood onset and adult onset SSc followed longitudinally at a single center[12]. In the largest study of its kind, another interesting classification issue in SSc arises. Of the 111 patients with symptom onset before the age of 16, almost half (44%) were diagnosed in adulthood. Thus the question arises, should this subgroup be included with the childhood onset or the adult onset diagnosis group? In this case, the definition of time zero is critical to classification. Time is the common denominator in many important outcomes such as incidence, period prevalence, disease duration, and time-to-event analyses, includ-

See Childhood onset SSc: Classification, clinical and serologic features, and survival in comparison with adult onset disease, *page 1004*

ing survival[13]. Thus the inaccurate specification of time zero can lead to a systematic deviation from the truth (bias). Important biases that may affect the validity of study results include *lead time bias* (early detection falsely appears to prolong survival), *length time bias* (screening overrepresents less aggressive disease), and most importantly, *misclassification bias* (systematic error in classifying a patient's exposure or disease status). *Neyman's prevalence-incidence bias* can occur when late evaluation of patients affected early in life misses fatal cases. This type of sampling bias can result in skewing of reported odds ratios in both case-control and cohort studies[14]. Individually or together, these biases can potentially affect the current study results by making the effect of the disease on outcomes larger or smaller than it really is.

Some investigators advocate that classification of patients should be determined at the time classification criteria are evaluated and met. Patients who develop symptoms in childhood but do not present to the medical system for diagnosis and management until adulthood would thus be classified as SSc of adulthood. Within this classification paradigm, symptom recognition by the child and parent as well as access to care issues may delay the time between disease onset and entry into the healthcare system. Scalapino, *et al* have addressed this classification dilemma by presenting 2 sets of results, a comparison of outcomes between childhood onset and adult onset disease patient subgroups, and a comparison of outcomes between childhood diagnosis and adult diagnosis patient subgroups.

This classification issue also applies to other rheumatic diseases including systemic lupus erythematosus, vasculitis, and even rheumatoid arthritis (RA). Age 16 years is an arbitrary classification threshold, with no particular biologic rationale. A 14-year-old patient with rheumatoid factor-positive polyarthritis who meets classification criteria and is seen by a rheumatologist is classified as having juvenile inflammatory arthritis (JIA), but if the same disease starts at age 16 years and 1 day, it is classified as RA. Under this paradigm, how does one classify a patient whose symptoms started at age 15 years, 9 months, but whose rheumatology appointment delayed diagnosis another 4 months — as JIA or RA? Similar classification issues occur with systemic JIA versus adult onset Still's disease.

As international research collaborations between pediatric and adult rheumatology centers increase, this aspect of classification will need to be addressed. Is it acceptable to retrospectively apply classification criteria? If so, how do we account for recall bias? Should time zero start when an individual is "classified" as having the disease by a healthcare professional? In this case, how do we account for access to care issues? Until this issue is resolved, investigators should clearly specify on what basis such study patients were classified. Since the specification of time is central to so many important outcome measures, only precise specification of grounds for classification will allow for comparisons across studies.

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