Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Validation of long-term wheelchair use as a surrogate for OI severity: usefulness in epidemiological studies using claims data

Winnie Liu

lwin@ohsu.edu

Oregon Health & Science University

Emily Holladay

University of Alabama at Birmingham

Salma Musaad

Baylor College of Medicine

Sina Sanei

Baylor College of Medicine

Lars Folkestad

Odense University Hospital

Jeffrey R. Curtis

University of Alabama at Birmingham

Eric Orwoll

Oregon Health & Science University

Research Article

Keywords:

Posted Date: November 22nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11681463/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

Osteogenesis imperfecta (OI) is a rare bone disorder underrepresented in large-scale epidemiological research. Large cohort studies using insurance claims databases and electronic health record (EHR) databases offer an opportunity to assemble and analyze large OI cohorts, but do not typically include information about OI severity as structured data elements. Wheelchair use can be identified from these administrative data. This study used a large, highly phenotyped cohort of people with OI to evaluate if wheelchair use is a suitable surrogate for OI severity.

Methods

We analyzed data from the Longitudinal Study of the Brittle Bone Disorders Consortium. OI clinical severity was determined using the Sillence classification. Wheelchair use was identified from a medical history questionnaire and the Gillette Functional Assessment Questionnaire Walking Scale (GFAS). We determined the proportion of people with type 1, 3 and 4 OI who reported wheelchair use.

Results

832 people with OI were included; 428 (51%) were Type 1 OI, 170 (21%) Type 3 and 234 (28%) Type 4. There were 510 children < 18 years (61%) and 322 adults (39%). In the group with type 3 OI, 86% reported wheelchair use (92% of adults). In those with type 4, 39% (32% of adults) used a wheelchair. Very few people with type 1 OI (4%) reported wheelchair use.

Conclusions

Wheelchair use is highly effective in differentiating people with type 3 OI from those with type 1 and identifies those with type 4 who are more severely affected, providing a reliable framework for population-level epidemiological and health service evaluations of osteogenesis imperfecta using administrative datasets.

Introduction

Osteogenesis imperfecta (OI) is a genetically heterogeneous, rare disorder caused by mutations in type I collagen genes or genes associated with type I collagen processing or function, or bone mineralization (1, 2). The clinical severity of OI is quite variable and is conventionally classified with the Sillence criteria (3). Using that approach, 60–75% of those with OI who survive the neonatal period have mild, non-deforming (type 1), 10–15% have progressively deforming (type 3), 15–25% have moderate OI (type 4), and a small number have more uncommon forms (4, 5).

Epidemiological studies of rare disorders are difficult because data from large cohorts are frequently unavailable. Information from administrative claims-based data and other administrative datasets (e.g. electronic health records [EHR]) can be extremely useful to assemble adequately powered cohorts, and this approach has been used quite productively in studies of OI (6, 7).

However, a challenge in using administrative data for studies of OI is the lack of information concerning OI clinical severity, which is linked to the degree of skeletal fragility and bone deformities. To remedy this problem, we developed methods to use claims information to identify long-term wheelchair use as a surrogate for severe OI (7). In those studies, we used the Merative MarketScan claims database, a large collection (~ 130M people) of de-identified US healthcare administrative insurance claims, and a random sample of Medicare beneficiaries, to assemble and analyze a cohort of 6475 patients with OI. We identified a sub-cohort of 1276 (20%) with evidence of long-term wheelchair use and who presumably had more severe OI. In this report, we used a large, clinically phenotyped cohort of individuals with OI to validate the hypothesis that wheelchair use adequately identifies people with more severe clinical forms of OI.

Methods

The Brittle Bone Disorders Consortium (BBDC) Longitudinal Study. The Longitudinal Study is part of the National Institutes of Health Rare Diseases Clinical Research Network (RDCRN) (NCT02432625) and is a longitudinal observational evaluation of children and adults with a clinical, molecular, or biochemical diagnosis of OI (8). The full study recruited 914 participants from 12 communities and medical centers between 2010 and 2023. OI severity was classified based on Sillence criteria. Extensive phenotyping was performed to characterize the participants' OI and other demographic and clinical traits. Data were collected across all sites in accordance with a manual of operations and managed by the RDCRN's Data Management and Coordinating Center. Data for current analyses were from 832 individuals with Sillence types 1, 3 and 4. We excluded data from 82 individuals with less common types of OI. This study was performed in accordance with the ethical standards in the Declaration of Helsinki and Health Insurance Portability and Accountability Act regulations. All participants provided informed, written consent and the study was approved by the Baylor College of Medicine Institutional Review Board.

Information on participants' mobility, physical function and wheelchair use was assessed at the initial clinic visit. The primary outcome assessed in these analyses was a simple question that was part of the medical history assessment, asking "Do you use a wheelchair? (yes/no)". An answer was provided by 824 participants. In addition, the Gillette Functional Assessment Questionnaire Walking Scale (GFAS) (9) was administered. The GFAS is a parent- or caregiver-completed ordinal instrument designed to measure everyday functional walking ability in which participants grade their ability on a 10-level scale from the most limited ("cannot take any steps at all") to the most unrestricted ("Walks, runs, and climbs on level and uneven terrain and does stairs without difficulty or assistance"). Questions 1–6 were considered indicative of wheelchair use and questions 9–10 indicative of no wheelchair use. Few participants

answered yes to questions 7–8 and were not used to categorize wheelchair use. Responses from 718 participants were analyzed.

2Data were descriptively characterized using mean (standard deviation) or frequency and percent. Differences between categorical variables were tested using the Chi square or Fisher's exact test. A 2-tailed p value was used to determine significance. Analyses were conducted using the SAS version 9.4 (SAS Institute, Inc., Cary, NC).

The study procedures were approved by the Institutional Review Boards of all participating clinical sites and informed consent was obtained from all participants or their legal guardians.

Results

The characteristics of the 832 BBDC Longitudinal Study participants included are shown in Table 1. There were 510 children < 18 years (61%) and 322 adults (39%) (age range 18–81 years); 428 (51%) were classified as type 1 OI, 170 (21%) as type 3 OI and 234 (28%) as type 4 OI.

Table 1
Cohort demographic information

Age, years (mean, SD)	**Type 1 (N = 428)**	**Type 3 (N = 170)**	**Type 4 (N = 234)**
	22 (18)	**14 (13)**	**18 (16)**
Female (%)	62	54	57
Age ≥ 18 years (%)	43	29	38
Race (% White)	88	79	82

The responses to the question "Do you use a wheelchair?" are shown in Fig. 1.

Across all ages, almost all participants with type 1 OI denied using a wheelchair, and a large majority (86%) of those with type 3 reported wheelchair use. About 1/3 of those with type 4 OI used a wheelchair. In adults, 92% of those with type 3 OI reported wheelchair use, while 99% of those with type 1 did not. Once again, adults with type 4 OI were intermediate (32% reported wheelchair use). Results were similar when excluding people ≤ 3 years who might not be expected to be ambulatory and thus not need a wheelchair.

Results from the analysis of GFAS responses were essentially the same as those using the medical history question (Fig. 2).

In the entire cohort, responses in 93% of those with type 1 OI indicated no wheelchair use, while 87% of those with type 3 did. In adults, responses from 97% with type 1 OI indicated no wheelchair use, and responses from 96% of those with type 3 OI suggested wheelchair use. In those with type 4 OI, responses in 35% (29% of adults) indicated wheelchair use. Of those who reported wheelchair use on the

medical history questionnaire, 77% were classified by GFAS as having a severe mobility limitation phenotype (categories 1–6) while only 8% who denied wheelchair use fell in those categories.

Discussion

To evaluate the effectiveness of using long-term wheelchair use as a surrogate for identifying more severely affected people with OI, we linked wheelchair use to clinical type of OI in a highly phenotyped cohort (BBDC). We found that wheelchair use was very uncommon in people with type 1 OI but was almost universal in those with type 3 OI. One third of people with type 4 OI reported wheelchair use, as would be expected since type 4 includes a wide spectrum of clinical severity, including some who have more significant mobility restrictions. Our results indicate that wheelchair use is very effective in identifying people with type 4 OI and likely identifies those with type 4 OI who are more physically limited.

A proportion, approximately 1/3, of those with type 4 OI reported wheelchair use and those who reported wheelchair use likely represent those who are more severely affected. This proportion of people with type 4 OI is generally consistent with available cohort data (10). Most (> 77%) of those with type 4 OI who reported wheelchair use were in GFAS categories 1–6 which is considered to indicate substantial mobility limitation, defined functionally by the absence of routine independent community ambulation. Conversely, only 8% of those who denied wheelchair use fell into those categories. Thus, wheelchair use was quite effective in identifying those with type 4 OI who had more severe physical disability. Overall, these data support wheelchair use as a means of identifying those with type 4 OI who have limited, non-community ambulation.

Administrative data sets can be effectively used to identify people who have wheelchairs. Wheelchair purchase, repair, and wheelchair-specific accessory claims provide face and construct validity for identifying wheelchair use, and these claims have been used in administrative claims studies of OI, including MarketScan and Medicare claims-based analyses, to ascertain wheelchair status or possession (11). Thus, insurance claims data can provide a reasonable proxy for at least some wheelchair use. Furthermore, claims-based wheelchair indicators have been strongly associated with independently assessed activities of daily living (ADL) dependency and functional impairment, and wheelchair Healthcare Common Procedure Coding System (HCPCS) claims have been among the strongest claims-based predictors of survey-measured frailty and mobility disability (12, 13). Together, these data support the contention that claims-based wheelchair indicators identify people who both have a wheelchair and have more severe mobility impairments. Thus, using insurance claims-based wheelchair indicators, we can legitimately identify people with OI who are more severely affected by mobility impairment.

The major strength of the study is the large, well-characterized BBDC data that explicitly include an assessment of wheelchair use as well as the GFAS questionnaire that not only identifies wheelchair use but allows us to link wheelchair use to levels of physical function. There are also caveats to consider. The GFAS is used primarily in children and there are fewer studies reporting its use in adults.

Nevertheless, the GFAS questions are quite clear concerning wheelchair use and physical activity and should be as applicable to adults as children. In addition, although using claims-based data to identify wheelchair possession is well-substantiated, we did not directly link the BBDC study population to an insurance claims data set to specifically test the concordance of claims-based wheelchair use to direct questionnaire-based evidence.

Large insurance claims and other administrative data sets can be extremely useful for the study of rare disease epidemiology. However, since current World Health Organization International Classification of Diseases codes do not reflect the clinical type or clinical severity of OI, there has been no established way to examine those research cohorts by OI clinical severity. The current results are important as they provide validation for using wheelchair claims to identify those with more severe OI (type 3 and more severely affected type 4), thus facilitating epidemiological studies that assess the impact of clinical severity on outcomes in OI.

Declarations

Acknowledgements

Support for the project was provided by institutional sources at Oregon Health & Science University. We would like to thank Sandesh Nagamani and Dianne Nguyen for help with data acquisition and study initiation. The research participants generously provided time and effort during the study, and research staff expertly conducted the protocol.

We acknowledge the contributions of current **Members of the Brittle Bone Disorders Consortium:** Brendan Lee, V. Reid Sutton, Sandesh C.S. Nagamani, Frank Rauch, Marie-Eve Robinson, Jean-Marc Retrouvey, Julia Cohen-Levy, Priyam Jani, Nadine Almpani, Janice Lee, Jeanne Franzone, Danielle Gomez, Karen Kruger, Peter Smith, Tracy Hart, Malinda Wu, Deborah Krakow, Eric Sung, Eric Orwoll, Lindsey Nicol, Winnie Liu, Cathleen Raggio, Laura Tosi, Danita Velasco, Bettina Willie, Maegen Wallace

We acknowledge the contributions of Former PIs of the BBDC, Francis Glorieux, Michael Bober, Gerald Harris, Eric Rush, Mahim Jain, Pamela Smith, and Paul Esposito.

We acknowledge all BBDC Research Coordinators who have contributed to the collection, management, and quality assurance of this dataset. Research Coordinators of the BBDC include Mary Mullins, Walaa Ali, Mahshid Azamian, Alicia Turner, Melanie Abrahamson, Angela Hornsten, Sam Alon, Sarah Gaunt, Angela Caudill, Jenny Goodwin, Elizabeth Strudthoff, Cassondra Brown, Katie Richardson, Sarah O'Neill, Isabella Wheeler, Emily Carney, Danqi Li, Austin Gillies, Andrew Pennington, Elaine Deval, Margaret Gross-King, Elizabeth Walker, Elizabeth Yonko, Erin Carter, Chloe DeRocher, Karen Dubose, Caitlin Brow, Michaela Durigova, Laura Rozo-Rojas, Fredrick Charbonneau, Dianne Nguyen.

Funding

Dr. Curtis receives salary support from NIAMS P30AR072583.

Dr. Musaad is funded in part with federal funds from the United States Department of Agriculture, Agricultural Research Service (USDA/ARS) under Cooperative Agreement No. 58-3092-5-008.

The Brittle Bone Disorders Consortium (BBDC) is part of the Rare Diseases Clinical Research Network (RDCRN), which is funded by the National Institutes of Health (NIH) and led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI). BBDC is funded under grant number U54AR068069 asa collaboration between NCATS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research (NIDCR), National Human Genome Research Institute (NHGRI), the Office of Research on Women's Health (ORWH), and the NIH Office of the Director (OD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was supported by the NIH RDCRN's DMCC at the Cincinnati Children's Hospital.

All RDCRN consortia are supported by the network's Data Management and Coordinating Center (DMCC) (U2CTR002818). Funding support for the DMCC is provided by the National Center for Advancing Translational Sciences (NCATS) and the National Institute of Neurological Disorders and Stroke (NINDS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the USDA.

Declaration of Competing Interests

W.L., E.H., S.M., S.S., L.F. have nothing to disclose. E.O. has been a consultant for Amgen, Angitia, and Ultragenyx. JC has been a consultant for Amgen and received research support from Amgen and Angitia.

Corresponding Author: Winnie Liu, MD, Oregon Health & Science University, 3181 SW Sam Jackson Park Road (CR113), Portland, OR 97239, USA. E-mail: lwin@ohsu.edu ORCID: https://orcid.org/0000-0002-2607-0336

Clinical trial:

Registry: ClinicalTrials.gov (https://www.clinicaltrials.gov/)

Trial registration number: NCT02432625

Date of registration: April 29, 2015 (the date the record was first submitted)

Ethics approval and consent to participate: This study was performed in accordance with the ethical standards in the Declaration of Helsinki and Health Insurance Portability and Accountability Act regulations. All participants provided informed, written consent and the study was approved by the Baylor College of Medicine Institutional Review Board.

Consent for publication

Written informed consent was obtained from all patients who completed the questionnaires.

Members of the Brittle Bone Disorders Consortium: Brendan Lee, V. Reid Sutton, Sandesh C.S. Nagamani, Frank Rauch, Marie-Eve Robinson, Jean-Marc Retrouvey, Julia Cohen-Levy, Priyam Jani, Nadine Almpani, Janice Lee, Jeanne Franzone, Danielle Gomez, Karen Kruger, Peter Smith, Tracy Hart, Malinda Wu, Deborah Krakow, Eric Sung, Eric Orwoll, Lindsey Nicol, Winnie Liu, Cathleen Raggio, Laura Tosi, Danita Velasco, Bettina Willie, Maegen Wallace

References

1. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet. 2016;387(10028):1657–71.
2. Jovanovic M, Marini JC. Update on the Genetics of Osteogenesis Imperfecta. Calcif Tissue Int. 2024;115(6):891–914.
3. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A. 2014;164A(6):1470–81.
4. Lindahl K, Åström E, Rubin CJ, Grigelioniene G, Malmgren B, Ljunggren Ö, et al. Genetic epidemiology, prevalence, and genotype-phenotype correlations in the Swedish population with osteogenesis imperfecta. Eur J Hum Genet. 2015;23(8):1042–50.
5. Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020;183(4):R95–R106.
6. Folkestad L, Hald JD, Ersbøll AK, Gram J, Hermann AP, Langdahl B, et al. Fracture Rates and Fracture Sites in Patients With Osteogenesis Imperfecta: A Nationwide Register-Based Cohort Study. J Bone Miner Res. 2017;32(1):125–34.
7. Liu W, Zhang J, Daigle S, Xie F, Liu Y, Folkestad L, et al. Rates and Pattern of Antifracture Drug Use in 6475 Adults and Children With Osteogenesis Imperfecta. J Clin Endocrinol Metab. 2026;111(3):e778–e86.
8. Rodriguez Celin M, Kruger KM, Caudill A, Murali CN, Nagamani SCS, Smith PA, et al. A multicenter study to evaluate pain characteristics in osteogenesis imperfecta. Am J Med Genet A. 2023;191(1):160–72.
9. Novacheck TF, Stout JL, Tervo R. Reliability and validity of the Gillette Functional Assessment Questionnaire as an outcome measure in children with walking disabilities. J Pediatr Orthop. 2000;20(1):75–81.
10. Kruger KM, Caudill A, Rodriguez Celin M, Nagamani SCS, Shapiro JR, Steiner RD, et al. Mobility in osteogenesis imperfecta: a multicenter North American study. Genet Med. 2019;21(10):2311–8.
11. Gooch KL, Audhya I, Ricchetti-Masterson K, Szabo SM. Current Challenges of Using Patient-Level Claims and Electronic Health Record Data for the Longitudinal Evaluation of Duchenne Muscular Dystrophy Outcomes. Adv Ther. 2024;41(9):3615–32.

12. Faurot KR, Jonsson Funk M, Pate V, Brookhart MA, Patrick A, Hanson LC, et al. Using claims data to predict dependency in activities of daily living as a proxy for frailty. Pharmacoepidemiol Drug Saf. 2015;24(1):59–66.
13. Mather HL, Bollens-Lund E, Husain M, Kelley AS. Candidate Claims-Based Indicators of Functional Impairment: An Exploration in a Sample of Medicare Beneficiaries. J Pain Symptom Manage. 2019;58(3):e8–e11.

Figures

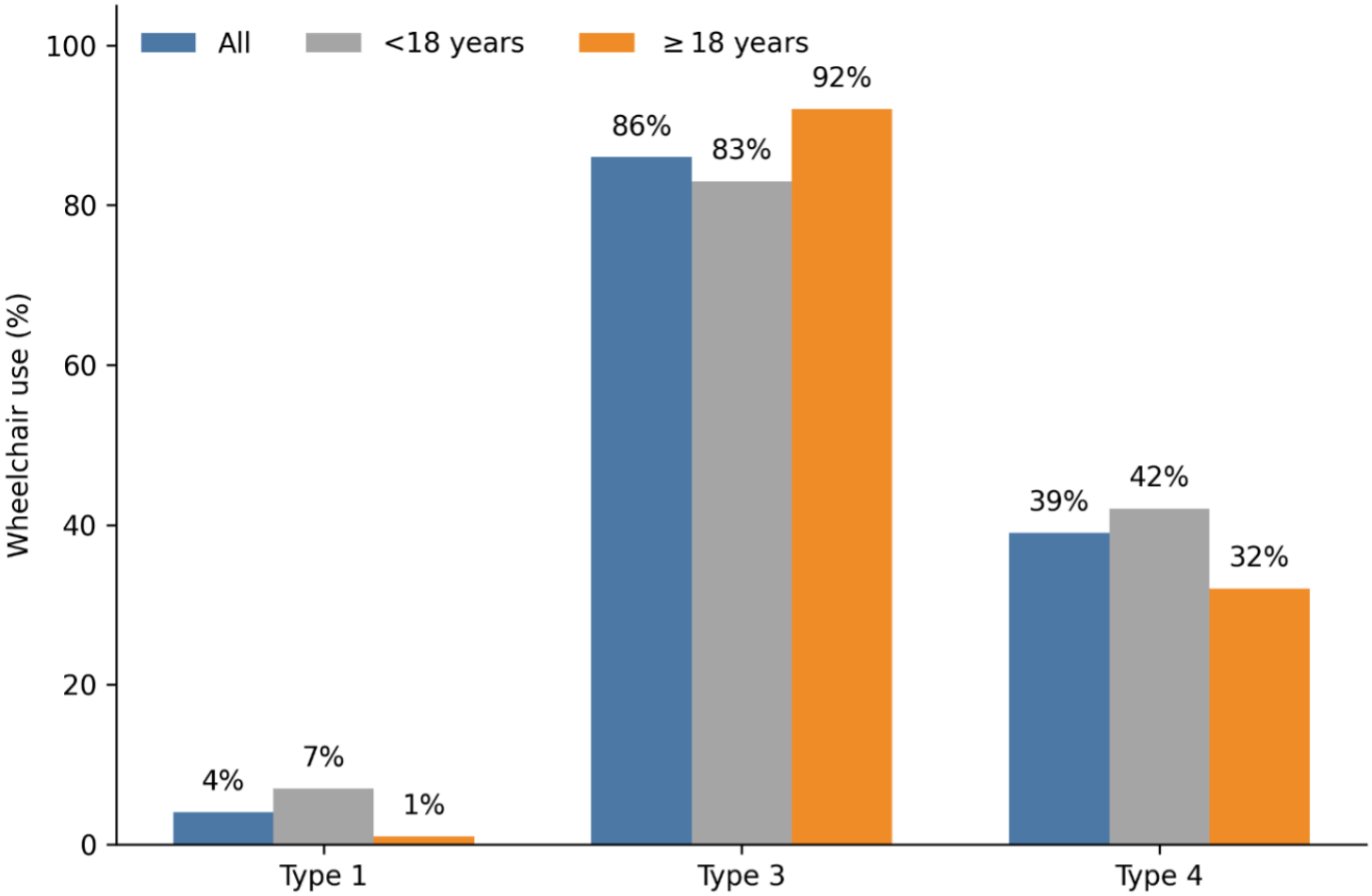


Figure 1

The proportion of people with OI who reported wheelchair use in the medical history questionnaire.

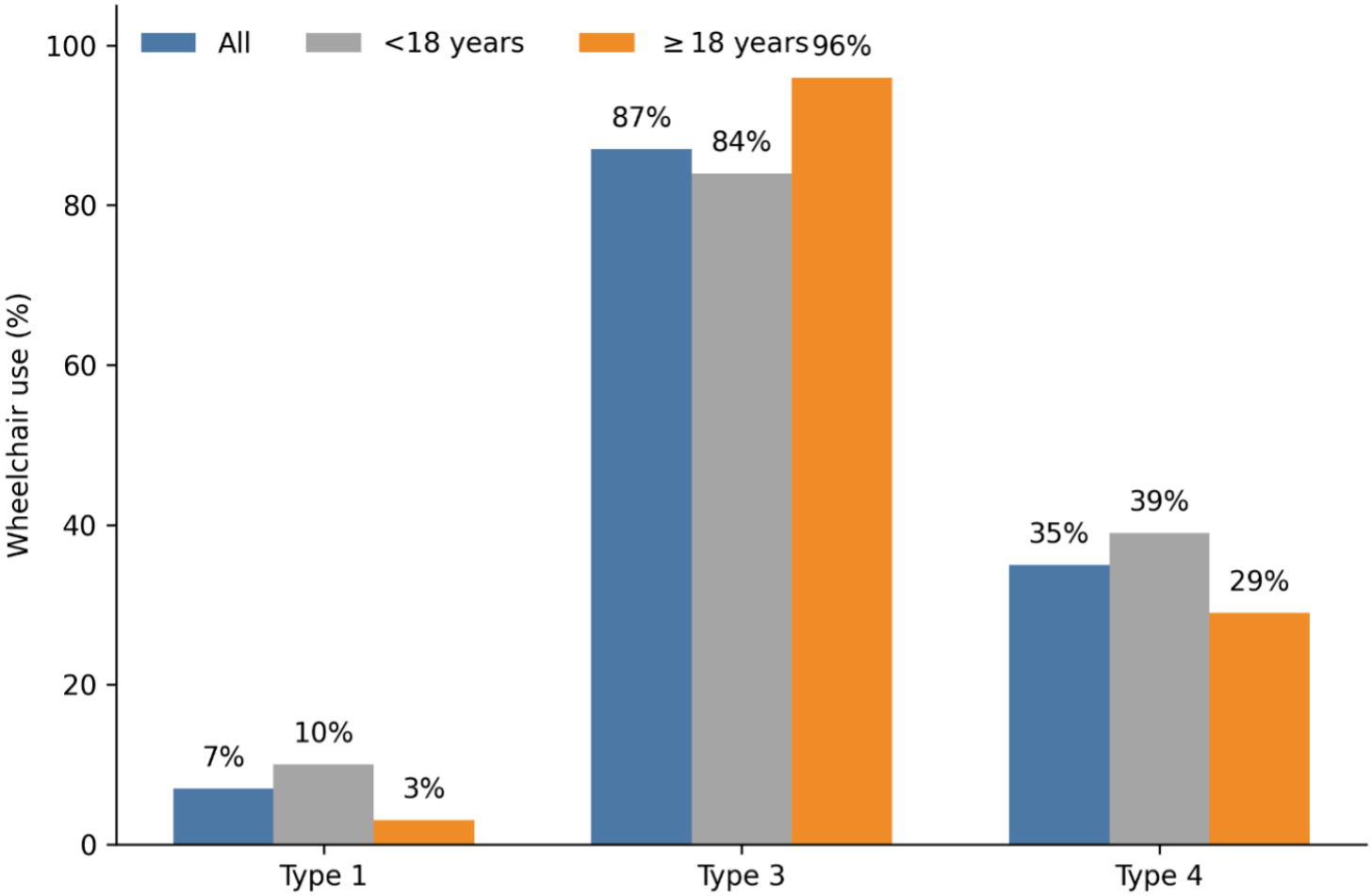


Figure 2

The proportion of people with OI who were considered likely to use a wheelchair from the GFAS questionnaire.