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ORIGINAL RESEARCH

Positive Predictive Value of Non-Traumatic Bleeding Diagnoses in the Danish National Patient Register

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Purpose: The majority of bleeding diagnoses in the Danish National Patient Registry have not been validated despite extensive use in epidemiological research. Therefore, we examined the positive predictive value (PPV) of non-traumatic bleeding diagnoses in the Danish National Patient Registry.

Study Design: Population-based validation study.

Patients and Methods: Based on a manual review of electronic medical records, we estimated the PPV of diagnostic coding (International Classification of Diseases, Tenth Revision (ICD-10)) for non-traumatic bleeding for all patients ≥65 years of age with any hospital contact in the North Denmark Region during March–December 2019 as registered in the Danish National Patient Registry. We calculated PPVs and associated 95% confidence intervals (CI) for non-traumatic bleeding diagnoses overall and stratified according to primary or secondary diagnosis, and according to major anatomical sites.

Results: A total of 907 electronic medical records were available for review. The population mean age was 79.33 years (standard deviation (SD)=7.73) and 57.6% were males. Primary bleeding diagnoses accounted for 766 of the records and 141 were secondary bleeding diagnoses. The overall PPV for bleeding diagnoses was 94.0% (95% CI: 92.3–95.4). The PPV was 98.7% (95% CI: 97.6–99.3) for the primary diagnoses and 68.8% (95% CI: 60.7–75.9) for the secondary diagnoses. When stratified according to subgroups of major anatomical sites, the PPVs ranged between 94.1% and 100% for the primary diagnoses, and between 53.8% and 100% for secondary diagnoses.

Conclusion: The overall validity of non-traumatic bleeding diagnoses in the Danish National Patient Registry is high and considered acceptable for epidemiological research. However, PPVs were substantially higher for primary than for secondary diagnosis.

Keywords: bleeding, epidemiology, validity, register-based research

Introduction

Nationwide administrative health registries are becoming increasingly utilized in post-marketing surveillance of drug safety since it is an efficient and inexpensive method to monitor clinical events associated with drug exposure. This is also the case in Denmark, where such registries constitute a significant research source as they contain an advantageously large amount of long-term longitudinal data with a high degree of coverage.[1–3] Data from health registries reflect clinical outcomes experienced by patients in a non-selected clinical practice setting, provided that the outcomes are appropriately identified and correctly coded.[4] Hence, the validity of the data in these registries is of great concern when working with register data, as the registration needs to be accurate for the data to be useful. The Danish National Patient Registry collects data on diagnoses from all admissions at Danish hospitals, and it is considered to be one of the most comprehensive of its kind, yet, the registry, just as other health registries, primarily serves administrative purposes; hence, the validity of diagnoses is known to vary.[5,6]

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Previous studies validating ICD bleeding codes have focused on validating specific bleeding diagnoses, eg, intracerebral hemorrhage,[7] but several diagnoses remain unvalidated and composite bleeding definitions including any hospital-related bleeding are often used in studies of drug safety.[8–13] As such, register-based studies of bleeding events might not adequately describe the extent of bleeding events, making it difficult to interpret results in and across safety studies.

Bleeding is one of the most common and serious adverse events of antithrombotic treatment and a frequent cause of hospital admission.[14–17] With an increased disease burden closely linked to the aging population and a corresponding increase in medication use, the need to assess effectiveness of treatments against the risk of bleeding events is central, both in clinical trials and in post-marketing surveillance studies.[16,18,19] Therefore, this study aims to provide estimates of positive predictive values (PPV) of International Classification of Diseases, Tenth Revision (ICD-10) codes for non-traumatic bleeding events registered during hospital admissions in the Danish National Patient Registry.

Materials and Methods

Setting and Data Source

The Danish healthcare system provides free universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals.[5] Denmark is divided into five regions, geographically, and each region is representative of the Danish population in terms of demography, socioeconomic characteristics, and healthcare use.[20] This study uses data from the North Denmark Region, where about 10% of the Danish population resides (0.59 million inhabitants).[21]

Data from the Danish healthcare system is collected in several national databases for administrative purposes and quality control. These databases are also utilized for research purposes, and all information obtained from the registries can be linked using the personal identification number provided to all permanent residents of Denmark at birth or migration.[22] The main registry with data on diagnoses is the Danish National Patient Registry. This registry has collected data on dates of admission and discharge as well as diagnoses from all Danish non-psychiatric hospitals since 1977 and on dates of emergency room and outpatient clinic visits since 1995.[5] All hospitals in Denmark report data in a standardized format, where a patient is discharged with one primary diagnosis and, optionally, up to several secondary diagnoses classified according to the ICD codes in the Danish National Patient Registry. The 10th revision of the ICD codes has been used in the Danish National Patient Registry since 1994.[5,6]

ICD-10 Codes for Non-Traumatic Bleeding

The data extraction for this study was done as part of the global Medication Without Harm initiative, which aims to describe the extent and characteristics of adverse events associated with the use of various prescription drugs.[23,24] As the initiative highlighted that the elderly are more susceptible to adverse outcomes,[24] the focus in the current study pertained to patients aged 65 years or older. To describe associations between bleeding requiring hospitalization and potential adverse drug events, a list of all non-traumatic ICD-10 bleeding codes (eg, codes indicative of perioperative or traumatic bleeding were removed) was compiled in collaboration between researchers and clinicians. This resulted in the inclusion of 40 ICD-10 codes, encompassing bleeding in the central nervous system, thorax and respiratory passages, gastrointestinal and intraabdominal, reproductive tract, urinary tract, and other bleeding locations. All ICD-10 codes used in the study are provided in Supporting Information Table S1.

Study Population

This was a population-based validation study of residents in the North Denmark Region ≥65 years of age with any hospital contact (inpatient, outpatient, or emergency department contacts) with an ICD-10 code for non-traumatic bleeding in the period of 1st March 2019 to 31st December 2019 recorded in the Danish National Patient Registry. We included patients with non-traumatic bleeding registered as the primary or secondary diagnostic code. We limited records to patients' first hospital contact with a bleeding event within the year 2019 coded as primary or secondary and excluded patients with more than one non-traumatic bleeding as a primary diagnostic code at one admission (Figure 1).

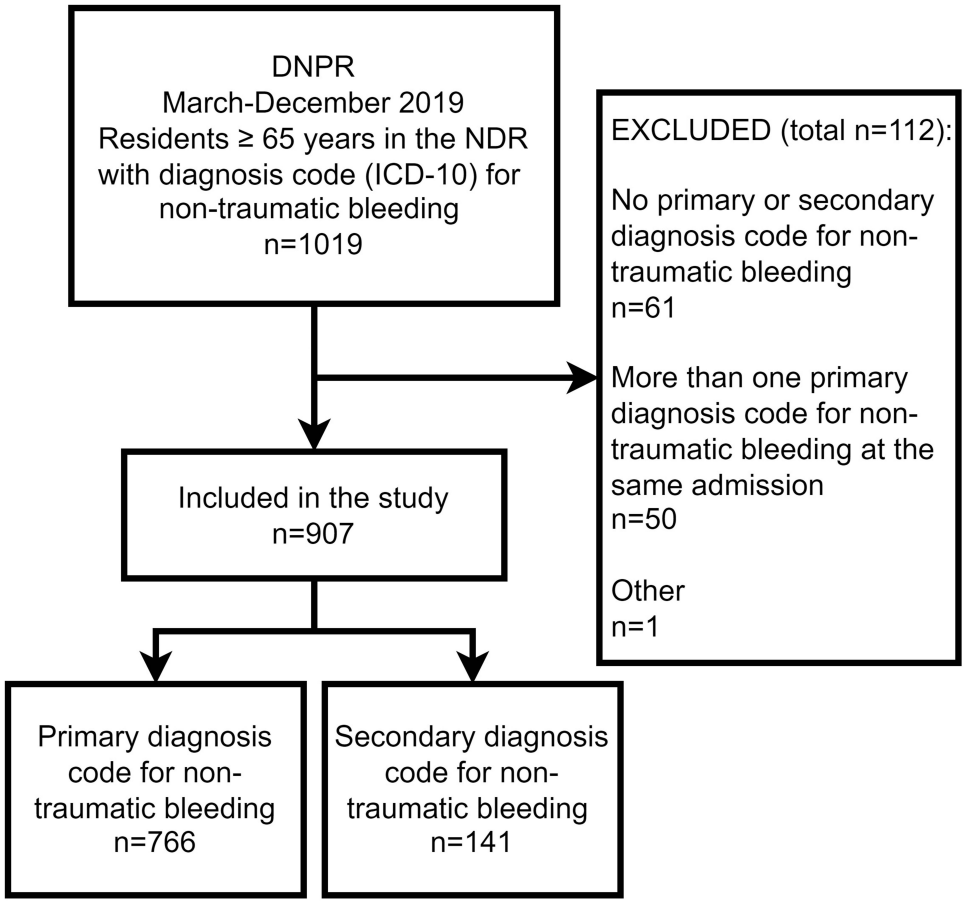

Figure 1 Identification of patient records for validation from the Danish National Patient Registry.
Abbreviations: DNPR, Danish National Patient Registry; NDR, North Denmark Region.

The inclusion of all eligible patients with non-traumatic bleedings in the study period resulted in a varying number of cases per ICD-10 code depending on how often different bleedings occur.

Validation Using Electronic Medical Record Review

Using the Danish Civil Personal Registration number, we linked electronic medical records to discharge diagnostic codes in the Danish National Patient Registry.[6,25] Electronic medical record review was used as the gold standard reference. Two researchers with medical training (MT and MBP) reviewed the electronic medical records and judged whether they could confirm the non-traumatic bleeding diagnosis coded in the Danish National Patient Registry. Information on sex, age, symptoms at admission, and antithrombotic drug use was collected using a structured abstraction form in REDCap (Research Electronic Data Capture, REDCap 10.6.26 – © 2022 Vanderbilt University, USA) hosted at the North Denmark Region to ensure consistency and security.

The entire electronic medical record was reviewed in all cases and each record underwent a comprehensive review for the presence of bleeding including relevant symptoms of bleeding and objective evidence of bleeding such as endoscopic results or imaging descriptions. All symptoms indicating bleeding and objective evidence of bleeding used in the study are provided in Supporting Information Table S2, where they are presented according to major anatomical location. The following criteria used for the validation of diagnosis codes were a modified version of criteria used in previous validation studies.[3,7] The diagnosis was considered confirmed if the medical record contained (1) description of relevant symptoms indicating bleeding prehospitalization or in-hospital or (2) description of objective findings of bleeding, as well as (3) accordance between the findings in (1) or (2) and the bleeding location from the discharge diagnostic code. The diagnosis in the Danish National Patient registry was judged unconfirmed if none of the

abovementioned criteria was fulfilled. If the reviewer was uncertain of the validity of an ICD-10 code, the other reviewer performed a second independent electronic medical record review. In case of disagreement, an agreement was reached collectively.

Statistical Analysis

We assessed the validity of the ICD-10 diagnostic codes of non-traumatic bleeding in the Danish National Patient registry by comparison with electronic medical record. We quantified its validity by computing PPVs and estimated the corresponding 95% confidence intervals (CIs) according to the Wilson score method.[26] PPV was the proportion of non-traumatic bleeding diagnoses identified in the Danish National Patient registry that could be confirmed in electronic medical records. The bleedings were divided into the following anatomical regions: the central nervous system, thorax and respiratory passages, gastrointestinal and intraabdominal, reproductive tract, urinary tract, and other bleeding locations. Several secondary analyses were performed. First, we divided the diagnoses according to the location of the bleeding and used an anatomically correct bleeding episode as the reference standard, eg, we considered a diagnosis of subarachnoid hemorrhage valid if a bleeding episode in the central nervous system was described in the electronic medical record. Second, we calculated separate PPVs for primary and secondary diagnoses, which were also calculated according to anatomical regions. Additionally, subgroup analyses based on sex and age below or above the mean age were performed. Finally, we calculated the PPV for users and non-users of antithrombotic drugs. In this study, antithrombotic drugs included the following drugs (ATC, Anatomical Therapeutic Chemical): vitamin K antagonists (B01AA), heparin group (B01AB), platelet aggregation inhibitors (B01AC), direct thrombin inhibitors (B01AE), and direct factor Xa inhibitors (B01AF).

All analyses were performed using Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.)

The Danish Patient Safety Authority approved the study according to Danish Health Care Act § 46, stk. 2 (record number: 31-1521-323). This study is in compliance with the Declaration of Helsinki and the General Data Protection Regulation, and it is a part of the North Denmark Region's record of processing activities (F2023-027). Per Danish law governing analysis of registry data, no approval was required from the Ethics Committee.

Results

Out of a total of 1019 patients ≥65 years of age with non-traumatic bleedings in the Danish National Patient Registry in 2019, 907 patients were included in this study. Table 1 displays patient characteristics (42.4% female, mean age 79 years). Of the 907 patients, 766 (84.5%) had non-traumatic bleeding as a primary diagnosis, and 141 (15.5%) had non-traumatic bleeding as a secondary diagnosis. Grouped by major anatomical sites, 168 were CNS bleedings, 102 were thorax and respiratory passage bleedings, 468 were gastrointestinal tract and intraabdominal bleedings, 10 were reproductive tract bleedings, 135 were urinary tract bleedings, and 24 were categorized as other bleedings (Table 2).

Non-traumatic bleeding was confirmed in 853 out of the 907 cases resulting in an overall PPV of 94.0% (95% CI: 92.3–95.4). The PPV of the primary diagnoses was 98.7% (95% CI: 97.6–99.3), whereas the PPV for the secondary diagnoses was 68.8% (95% CI: 60.7–75.9). The PPVs ranged between 94.1% and 100% across anatomical sites for the primary diagnoses, and between 53.8% and 100% for the secondary diagnoses. The PPVs were consistent within subgroups of age and sex. The PPV was high for both users (95.2% (95% CI: 93.3–99.6)) and non-users (91.4% (95% CI: 87.6–94.1)) of antithrombotic drugs (Table 2).

There were 54 cases (10 primary diagnoses and 41 secondary diagnoses), where the electronic medical record review did not confirm the ICD-10 bleeding code. The study found three different types of errors in the unconfirmed cases: (1) inaccuracy when choosing diagnosis (n=22), (2) old bleeding event or scheduled follow-up (n=3), and (3) no bleeding event (n=29).

Table 1 Patient Characteristics at Admission

Patients in total	907
Age, mean (SD), y	79.33 (7.73)
Females, % (n)	42.4% (385)
Type of encounter, % (n)	
Emergency department	20.4% (185)
Hospitalization	79.6% (722)
Comorbidities, % (n)	
Diabetes mellitus	50.3% (456)
Hypertension	19.5% (177)
Ischemic heart disease	11.8% (107)
Cerebrovascular event	17.8% (161)
Chronic obstructive pulmonary disease	16.6% (151)
Chronic kidney disease	8.7% (79)
Chronic liver disease	1.7% (15)
Antithrombotic drug users, % (n)	69.1% (627)

Abbreviation: SD, Standard deviation.

Table 2 Positive Predictive Values (PPV) with 95% Confidence Interval (CI) of Non-Traumatic Bleeding ICD-10 Diagnoses Overall and by Subgroups

	N	**Confirmed**	**PPV (%)**	**95% CI**
All cases	907	853	94.0	92.3–95.4
Type of diagnosis				
Primary diagnosis	766	756	98.7	97.6–99.3
Secondary diagnosis	141	97	68.8	60.7–75.9
Age (years)				
66–79.33 (below mean age)	487	459	94.3	91.8–96.0
>79.33 (above mean age)	420	394	93.8	91.1–95.7
Sex				
Male	522	496	95.0	92.8–96.6
Female	385	357	92.7	89.7–94.9
Antithrombotic drug users				
Users	627	597	95.2	93.3–96.6
Non-users	280	256	91.4	87.6–94.1

(*Continued*)

Table 2 (Continued).

	N	Confirmed	PPV (%)	95% CI
Major anatomical sites				
Central nervous system				
All cases	168	156	92.9	87.8–95.9
Primary diagnosis	151	145	96.0	91.6–98.2
Secondary diagnosis	17	11	64.7	41.3–82.7
Thorax and respiratory passages				
All cases	102	96	94.1	87.8–97.3
Primary diagnosis	78	78	100.0	95.3–100.0
Secondary diagnosis	24	18	75.0	55.1–88.0
Gastrointestinal and intraabdominal				
All cases	468	434	92.7	90.0–94.8
Primary diagnosis	403	399	99.0	97.5–99.6
Secondary diagnosis	65	35	53.8	41.8–65.4
Reproductive tract				
All cases**	10	10	100.0	72.2–100.0
Primary diagnosis	–	–	100.0	67.6–100.0
Secondary diagnosis	–	–	100.0	34.2–100.0
Urinary tract				
All cases	135	134	99.3	95.9–99.9
Primary diagnosis	105	105	100.0	96.5–99.4
Secondary diagnosis	30	29	96.7	83.3–99.4
Other bleeding location*				
All cases**	24	23	95.8	79.8–99.3
Primary diagnosis	–	–	100.0	84.5–100.0
Secondary diagnosis	–	–	66.7	20.8–93.9

Notes: *The category "Other bleeding location" included bleedings not specified to major anatomical regions such as bleeding from a leg wound. **Data on the distribution of primary and secondary diagnoses not disclosed due to a small number of observations.

Abbreviations: PPV, Positive Predictive value; ICD, International Classification of Diseases; CI, Confidence Interval.

Discussion

In this validation study, we found that diagnoses of non-traumatic bleedings captured in the Danish National Patient Registry were generally valid with an overall PPV of 94.0%. The differentiation between primary and secondary diagnosis was of importance, as primary diagnosis of non-traumatic bleedings had a high PPV of 98.7% compared with a PPV of 68.8% for secondary diagnoses. The results were consistent across anatomical locations, age, sex, and use of antithrombotic drugs, all with overall PPVs >90%.

This is the first validation study to include a wide range of non-traumatic bleeding diagnoses in the Danish National Patient Registry. Performance of codes according to bleeding location was overall high, but code performance was substantially influenced by the diagnosis being primary or secondary with PPVs for secondary diagnosis codes ranging as low as 54% for bleeding in the gastrointestinal tract, indicating that caution must be used when including secondary diagnoses. This variation in the validity of primary and secondary diagnoses is in line with previous validation studies of bleeding and other diagnosis codes.[1,3,27,28] The lower accuracy of secondary diagnoses might arise through the definition of primary and secondary diagnoses, as the primary diagnosis has to describe the primary event for each patient contact, while secondary diagnoses are optional.[5] As such, another level of attention might be given to primary diagnoses, which might generate the variation in PPVs for primary and secondary diagnoses.

Comparing our results with those of other validation studies is limited as previous studies have evaluated more narrow sets of specific bleeding codes. To our knowledge, only one study has validated many of the same bleeding diagnoses as in the present study. The study was conducted in the US (2019) and found an overall PPV of 74.7% for ICD-10 bleeding diagnosis codes in 563 anticoagulant drug users,[3] which is lower than the PPV from the present study. Both studies used data from recent years and had some differences in study populations as our study included patients ≥65 years, while the other study included patients ≥20 years. In addition, all our patients were not, contrary to the US study, anticoagulant users, but PPV for antithrombotic users in the present study was also high compared to the US study.[3] The differences in PPVs may be explained by differences in validation criteria, as the US study only validated diagnosis, where objective evidence of bleeding was present and where the bleeding could be ascertained to anticoagulant drugs. These criteria differ from those used in this study, as symptoms of bleeding prehospitalization or in-hospital were enough to validate a diagnosis, and we did not include information on antithrombotic drug use in the validation process. This could contribute to the higher PPVs found in this study. Yet, results from one country may not be generalizable to other countries, where coding systems and diagnostics may differ, making direct comparisons difficult.[1]

Some specific bleeding codes have been validated in previous studies. Recently, Danish studies have reported PPVs for diagnosis codes in the Danish National Patient Registry for intracerebral hemorrhage of 73.1–75.0%,[7,29,30] for subarachnoid hemorrhage of 60.6–63.8%,[30,31] and for non-traumatic subdural hematoma of 62%.[28] As such, a higher PPV of 92.9% for bleeding in the central nervous system was found in this study. Of the aforementioned studies, one reevaluated original brain imaging to confirm the bleeding.[28] This was not done in the present study, which could have caused an overestimation of confirmed central nervous system bleedings. However, as in many of the other studies, descriptions of brain imaging in the medical record were used in the validation of the present study and as such, this might not explain the higher PPV of the present study. Moreover, age might have influenced the PPV in the present study since only one of the recent studies had a study population of only older adults and elders as in the present study.[30] However, two studies on intracerebral bleeding investigated PPV in different age groups, and they found no significant difference in PPV stratified by age.[7,29]

The overall higher PPVs of the present study might be in part explained by the fact that a thorough review of the entire electronic medical record was done in all cases in the present study, unlike some other studies[7,25,29,32] which validated diagnoses through discharge summaries and brain scan reports and only, in cases of doubt, reviewed the full medical record. As such, a review of full medical records might result in higher PPVs that more accurately reflect the use of ICD-10 codes to describe non-traumatic bleeding in registries such as the Danish National Patient Registry. Nonetheless, one study compared the use of minimal data (discharge records and brain scan) to the use of all available information when validating the type and location of intracerebral hemorrhages and found the use of minimal data sufficient for the ascertainment of the diagnosis.[29] As such, the higher PPV in the present study may be explained by increased awareness of correct coding or improved availability of diagnostic modalities, eg, CT and MRI technologies available in all hospitals with this type of patient.[5]

Three previous Danish studies have investigated the use of ICD-10 codes for gastrointestinal bleeding in the Danish National Patient Registry. Two of the studies validated ulcer disease codes (K25-K28) and reported PPVs of 94–95.6%.[32,33] This is in line with the results of our study, which reported an overall PPV of 92.7% for gastrointestinal and intraabdominal bleedings. The third study reported a PPV of 70% for upper gastrointestinal bleeding, and it included many of the ICD-10 codes for gastrointestinal bleedings also used in the present study.[2] The study is a multinational

validation study, which also investigates drugs related to gastrointestinal bleeding risk, but they did not report their validation criteria.[2] We are unaware of any other validation studies investigating any of the other bleeding codes included in this study.

In the cases of unconfirmed diagnoses, the three types of errors observed in this study are important to consider when designing new studies. Especially, the second type of incorrect registrations, where medical record review revealed scheduled follow-ups appearing as new cases in the Danish National Patient Registry. This could be a result of registration inaccuracy or a lack of more appropriate registration options. The latter is supported by the fact that this type of error was also seen in a Danish validation study of bleeding in the central nervous system.[31] This type of error warrants caution especially if repeated clinical events are studied, such as bleeding recurrence in the same anatomical site.

High data quality of health registries is essential to ensure that correct assumptions can be made about a cohort, which is why the Danish National Patient Registry is continuously evaluated.[31] The results of this study showed that the information on non-traumatic bleeding available in the Danish National Patient Registry is overall reliable, providing meaningful information on the quality and usefulness of the Danish National Patient Registry. This supports the dissemination and further use of registry research to investigate bleeding events and the study results presented in Table 2 may help researchers choose ICD-10 codes that suit their research purposes, despite this study not differentiating between major and minor bleedings as otherwise sometimes applied in the medical literature.[8,11,34]

Strengths and Limitations

The strength of this study was the inclusion of a large number of non-traumatic bleeding diagnoses leading to hospitalization. Also, all the diagnoses were validated based on predefined criteria and all electronic medical records underwent thorough review for validation of the bleeding diagnosis. However, sensitivity, specificity, and negative predictive values could not be calculated due to the design of the study as the data were sampled from the diagnosis codes of interest.

The basis of our study was a WHO initiative ("Medication Without Harm") and restricted to patients >65 years, but we consider it unlikely that the validity of non-traumatic ICD codes is markedly different among younger individuals. Indeed, the PPV was high in all prespecified subgroups in this study.

Data were extracted regardless of whether patients had a history of bleeding as reflected by previous ICD-codes for non-traumatic bleeding, and we were therefore not able to determine if the bleeding event was an incident or a recurrent bleeding event, events for which the PPV of other cardiovascular events is known to vary.[1]

Data were restricted to North Denmark Region, but this region is generally representative of the general Danish population, and we consider it unlikely that there are substantial differences in physicians' coding practice across regions.[20]

Conclusion

The positive predictive value of ICD-10 codes for non-traumatic bleeding diagnoses in the Danish National Patient Registry is overall high and acceptable for use in research, but caution is warranted when including secondary ICD-10 codes.

Abbreviations

ATC, Anatomical Therapeutic Chemical; CI, Confidence interval; CT, Computerized tomography; DNPR, Danish National Patient Registry; DK, Denmark; ICD-10, International Classification of Diseases, Tenth Revision; MRI, Magnetic resonance imaging; NDR, North Denmark Region; REDCap, Research Electronic Data Capture; SD, Standard deviation.

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Disclosure

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