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Comparison of Patients with Hospital-Recorded Nephrotic Syndrome and Patients with Nephrotic Proteinuria and Hypoalbuminemia: A Nationwide Study in Denmark

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Key Points

- Only a minority of patients with the biochemical features of nephrotic syndrome (NS) receive hospital diagnoses specific to NS.
- Patients identified with hospital-recorded NS are considerably different from those with biochemical features of NS.
- Laboratory databases should complement hospital databases to fully elucidate the burden of NS and the prognosis of patients with NS.

Abstract

Background Registry-based studies of nephrotic syndrome (NS) may only include a subset of patients with biochemical features of NS. To address this, we compared patients with laboratory-recorded nephrotic proteinuria and hypoalbuminemia to patients with hospital-recorded NS.

Methods We identified adult patients with first-time hospital-recorded NS (inpatients, outpatients, or emergency-room visitors) in the Danish National Patient Registry and compared them with adults with first-time recorded nephrotic proteinuria and hypoalbuminemia in Danish laboratory databases during 2004–2018, defining the date of admission or laboratory findings as the index date. We characterized these cohorts by demographics, comorbidity, medication use, and laboratory and histopathologic findings.

Results We identified 1139 patients with hospital-recorded NS and 5268 patients with nephrotic proteinuria and hypoalbuminemia; of these, 760 patients were identified in both cohorts. Within 1 year of the first record of nephrotic proteinuria and hypoalbuminemia, 18% had recorded hospital diagnoses indicating the presence of NS, and 87% had diagnoses reflecting any kind of nephropathy. Among patients identified with nephrotic proteinuria and hypoalbuminemia, their most recent eGFR was substantially lower (median of 35 versus 61 ml/min per 1.73 m^2), fewer underwent kidney biopsies around the index date (34% versus 61%), and the prevalence of thromboembolic disease (25% versus 17%) and diabetes (39% versus 18%) was higher when compared with patients with hospital-recorded NS.

Conclusions Patients with nephrotic proteinuria and hypoalbuminemia are five-fold more common than patients with hospital-recorded NS, and they have a lower eGFR and more comorbidities. Selective and incomplete recording of NS may be an important issue when designing and interpreting studies of risks and prognosis of NS.

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Introduction

Nephrotic syndrome (NS) is a clinical diagnosis defined by biochemical criteria of nephrotic proteinuria (>3.5 g/d), hypoalbuminemia, and the presence of edema (1,2). Data on the occurrence and prognosis of NS in adults are limited (3), and previous epidemiologic studies of NS have focused on patients with NS recorded in hospital or pathology databases (4–10). However, NS can present insidiously, and patients may seek the help of a range of specialists before receiving specialist care from hospital doctors. Furthermore, hospital diagnoses may suffer from incomplete and selected reporting if dependent on the referral for a kidney biopsy, or if the underlying disease is recorded instead of NS in selected groups. Therefore, it is likely that the current epidemiologic findings on NS may apply only to a selected group of patients with NS, and that the occurrence of NS may be underestimated. Because the NS diagnosis is highly dependent on the identification of nephrotic proteinuria and hypoalbuminemia, laboratory databases may be useful to identify patients with the most fundamental features of NS (11).

To address this issue, from Danish medical databases, we identified patients with (*1*) first-time hospital-recorded NS, or (2) first-time recorded nephrotic proteinuria and hypoalbuminemia, to characterize and compare these cohorts on baseline demographics, comorbidity burden, use of medication, laboratory findings, and histopathologic kidney biopsy specimen findings. To examine the timing and completeness of hospital-recorded diagnoses of NS, we also examined if and when patients with first-time hospital-recorded NS also had a first recorded nephrotic proteinuria and hypoalbuminemia, and *vice versa*.

Materials and methods

Setting

We used nationwide, routinely collected, data from Danish health care registries. The Danish health care system is tax funded with no user payment on inpatient, outpatient, emergency-room, and laboratory services, increasing the accessibility and minimizing the selection of health care users (12,13). Individual-level information across databases was linked using the unambiguous personal identifier of each Danish resident from the Civil Registration System (14).

Study Participants

We sampled two potentially overlapping cohorts including adults (≥18 years) from the five Danish regions (Central and North Denmark Region during 2004–2018; and Southern Denmark, Zealand, and the Capital Region during 2016–2018; Supplemental Figure 1).

The first cohort included patients with first-time hospital-recorded NS in The Danish National Patient Registry (15), which includes details on inpatients, outpatients, or emergency-room visitors (either primary or secondary discharge diagnoses of NS were included; Supplemental Appendix, co debook 1). Date of admission or first outpatient visit was defined as the index date.

The second cohort included patients with first-time recorded nephrotic proteinuria and hypoalbuminemia, measured no more than 1 day apart in their laboratory records. Laboratory records were retrieved from the Clinical Laboratory Information System Research Database at Aarhus University (which covers the Central and North Denmark Region) and the Register of Laboratory Results for Research (which covers Southern Denmark, North Denmark, Zealand, and the Capital Region) (Supplemental Figure 1) (13,16). Laboratory records included detailed information on all laboratory tests from general practice, outpatient clinics, emergency rooms, and within the hospital, which were analyzed in hospital laborat ories (13). Nephrotic proteinuria was defined as spot urine albumin-creatinine ratio of >220 mg/mmol, urine albumin excretion rate of >2.2 g/d, spot urine protein-creatinine ratio of >350 mg/mmol, or urine protein excretion rate of >3.5 g/d. Hypoalbuminemia was defined as plasma albumin (p-albumin) of <36 g/L in persons <70 years, and <34 g/L in persons ≥70 years (Supplemental Appendix, codebook 2) (11,17,18). We excluded women with hospital-recorded pregnancy in both cohorts because nephrotic proteinuria and hypoalbuminemia in pregnancy may reflect preeclampsia rather than NS (Supplemental Appendix, codebook 3). The cohort inclusion flow is provided in Supplemental Figure 2.

Covariates

For each patient, we obtained data on hospital-recorded prior kidney disease and comorbidity, recorded during the 10 years before the index date in the Danish National Patient Registry (Supplemental Appendix, codebook 4), and data on kidney transplantation at any time before the index date (Supplemental Appendix, codebook 5).

The most recent plasma creatinine measurement before the index date was obtained to compute baseline eGFR (Supplemental Appendix, codebook 2) using the Chronic Kidney Disease Epidemiology Collaboration formula without correction for race (19). Because eGFR does not accurately reflect kidney function when GFR is not stable, only outpatient plasma creatinine measurements were included (*i.e.*, excluding measurements during inpatient stay or emergency-room visits).

From the National Prescription Registry (20), we assessed if patients had filled prescriptions for specified types of medication at outpatient pharmacies during the 365 days before the index date (Supplemental Appendix, codebook 6). To characterize the severity of NS, we identified the highest urine albumin and protein levels and the lowest p-albumin recorded in laboratory records from 31 days before to 31 days after the index date.

Finally, histopathologic findings in kidney biopsy specimens from 6 months before to 6 months after the index date were obtained from the National Pathology Registry (Supplemental Appendix, codebook 7) (21).

Statistical Analyses

We characterized patients according to sex, median age in years (with interquartile range [IQR]), age group (18–49, 50–64, or ≥65 years), time period (2004–2006, 2007–2009, 2010–2012, 2013–2015, 2016–2018), prior kidney disease, comorbidity, kidney transplants, and filled prescriptions.

For all laboratory tests, we tabulated the proportion of patients with available tests, the median time from the recorded test in days (with IQR), and the median of the test results (with IQR).

Among those with kidney biopsies, we calculated the proportion with specific histopathologic findings within 6 months of the index date, allowing each person to contribute with findings in more than one histopathologic category.

To examine the timing of NS diagnoses in patients with hospital-recorded NS, we plotted the cumulative incidence proportions of first-recorded proteinuria tests, first-recorded nephrotic proteinuria, and first-recorded nephrotic proteinuria and hypoalbuminemia from 1 year before to 1 year after the index date.

To describe how many received a hospital diagnosis compatible with NS among patients with nephrotic proteinuria and hypoalbuminemia, we plotted the cumulative incidence proportions of first-diagnosed NS, any glomerular disease, or any nephropathy from 1 year before to 1 year after the index date (Supplemental Appendix, codebook 8).

In supplementary analyses, the overlap between patients included in the cohorts was illustrated in a Venn diagram. For patients included in only one or both of the cohorts, respectively, we tabulated characteristics of age, sex, comorbidity, medication, and laboratory findings, defining the index date as the date where the patients first fulfilled the inclusion criteria for any of the cohorts. To explore why some patients were included only in the hospital-recorded NS cohort, we examined if they had nephrotic proteinuria and hypoalbuminemia recorded before the study period, if they had nephrotic proteinuria and hypoalbuminemia recordings >1 (but <7) days apart, or if they had a recorded hypoalbuminemia with proteinuria no more than 10% below the nephrotic-range cutoff.

The study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/812). According to Danish legislation, no approval from an ethics committee or informed consent from patients is required for registry-based studies.

Data were extracted with SAS version 9.4 (SAS Institute, Cary, NC), and data management and analyses were conducted using R version 3.5.2.

Results

We identified 1139 adults with first-time hospital-recorded NS, and 5268 adults with first-time nephrotic proteinuria and hypoalbuminemia; of these, 760 patients were included in both cohorts (Table 1). This did not include the 33 (3%) pregnant women with hospital-recorded NS and 666 (11%) pregnant women with first-time nephrotic proteinuria and hypoalbuminemia (Supplemental Figure 2). More than half of the patients were men, and the age distribution was similar in the two cohorts.

Only 16 (1%) of those with diagnosed NS had a kidney transplant before the index date, compared with 337 (6%) of those with nephrotic proteinuria and hypoalbuminemia. GN (excluding NS), chronic pulmonary disease, diabetes, and nonhematologic and hematologic cancer were equally common in both cohorts, but more patients with nephrotic proteinuria and hypoalbuminemia had prior acute kidney disease or CKD (37% versus 15%), diabetes (39% versus 18%), congestive heart failure (9% versus 6%), or thromboembolic disease (25% versus 17%), compared with patients with hospital-recorded NS (Table 1). Also, use of antidiabetics and antihypertensive drugs was more common in patients with nephrotic proteinuria and hypoalbuminemia than in patients with hospital-recorded NS, whereas use of glucocorticoids and immunosuppressants was comparable (Table 1).

Almost all patients with hospital-recorded NS (95%) or nephrotic proteinuria and hypoalbuminemia (99%) had an outpatient plasma creatinine recorded before the index date. The most recent eGFR was substantially lower in those with nephrotic proteinuria and hypoalbuminemia (median [IQR] eGFR, 35 [17–65] ml/min per 1.73 m^2) than in those with hospital-recorded NS (median [IQR] eGFR, 61 [34–87] ml/min per 1.73 m^2) (Table 1).

The highest recorded albuminuria and proteinuria levels within a month from the index date were slightly higher in patients with hospital-recorded NS (*e.g.*, median [IQR] albumin-creatinine ratio, 468 [224–736] mg/mmol) than in those with nephrotic proteinuria and hypoalbuminemia (*e.g.*, median [IQR] albumin-creatinine ratio, 348 [262–527] mg/mmol). There was no difference in the proportions of patients with an albumin or protein excretion rate test from urine collection. Furthermore, hypoalbuminemia was more severe in those with a hospital-recorded NS (median [IQR] p-albumin, 23 [17–30] g/L) than in those with nephrotic proteinuria and hypoalbuminemia (median [IQR] p-albumin, 29 [24–32] g/L) (Table 2).

Within 6 months of the index date, 61% of patients with hospital-recorded NS and 34% of patients with nephrotic proteinuria and hypoalbuminemia had a kidney biopsy (Table 1). The frequency of different histopathologic findings was comparable in the two cohorts, with the most common findings being minimal change disease (27% versus 21%), "other/unspecified GN and fibrosis" (40% versus 49%), membranous nephropathy (22% versus 13%), mesangioproliferative glomerulopathy (14% versus 14%), and focal segmental glomerulosclerosis (11% versus 10%) (Table 3). Of note, a smaller proportion of patients with diabetes had kidney biopsies compared with other patients (43% among patients with diabetes and hospital-recorded NS, and 15% among patients with diabetes and nephrotic proteinuria and hypoalbuminemia).

At 1 year before the index date, 44% of patients with nephrotic proteinuria and hypoalbuminemia had a reported hospital diagnosis reflecting any nephropathy, which increased to 70% at the index date and 87% 1 year after the index date (Figure 1). Correspondingly, the proportion of patients with a reported diagnosis specific to NS increased from 4% at 1 year before the index date, to 10% at the index date, and 18% 1 year after the index date.

Among patients with available albuminuria or proteinuria and p-albumin tests, the majority had first-recorded nephrotic proteinuria and hypoalbuminemia close to the index date (Figure 2).

In supplementary analyses, we identified 760 patients with both first-time reported hospital diagnosis of NS and first-time nephrotic proteinuria and hypoalbuminemia within the study period, whereas 379 patients had only hospital-recorded NS, and 4508 patients had only nephrotic proteinuria and hypoalbuminemia (Supplemental Figure 3). Patients included with only a hospital-recorded NS were comparable with those included in both cohorts with respect to age, sex, comorbidity, use of medication, and level of most recent eGFR (Supplemental Table 1). The majority of the 379

Table 1. Characteristics of 1139 patients identified with first-time hospital-recorded nephrotic syndrome in the Danish National Patient Registry, and of 5268 patients with first-time recorded nephrotic proteinuria and hypoalbuminemia identified in Danish Laboratory information systems during 2004–2018

Characteristic	Patients with Hospital-Recorded NS	Patients with Nephrotic Proteinuria and Hypoalbuminemia
Overall, *n* (%)	1139 (100)	5268 (100)
Male sex, *n* (%)	682 (60)	3355 (64)
Age in years, median (IQR)	60 (45–73)	63 (50–72)
By age group, *n* (%)		
18–49 yr	361 (32)	1329 (25)
50–64 yr	310 (27)	1646 (31)
≥65 yr	468 (41)	2293 (44)
By period, *n* (%)		
2004–2006	127 (11)	414 (8)
2007–2009	124 (11)	316 (6)
2010–2012	166 (15)	550 (10)
2013–2015	168 (15)	947 (18)
2016–2018[a]	554 (49)	3041 (58)
Hospital-recorded kidney disease during 10 yr before index date, *n* (%)		
GN (excluding nephrotic syndrome)	109 (10)	538 (10)
Renal tubulointerstitial diseases	41 (4)	391 (7)
AKI and or CKD	66 (15)	1930 (37)
Cystic kidney disease	<5	139 (3)
Hypertension with nephropathy	14 (1)	155 (3)
Diabetic nephropathy	55 (5)	750 (14)
Hospital-recorded comorbidity during 10 yr before index date, *n* (%)		
Diabetes	206 (18)	2032 (39)
Chronic liver disease	29 (3)	163 (3)
Chronic pulmonary disease	114 (10)	580 (11)
Connective tissue disease	67 (6)	402 (8)
Congestive heart failure	72 (6)	458 (9)
Thromboembolic disease	192 (17)	1328 (25)
Nonhematologic cancer (excluding nonmelanoma skin cancer)	89 (8)	485 (9)
Hematologic cancer	42 (4)	149 (3)
Filled prescriptions within 365 d before index date, *n* (%)		
Antidiabetics	203 (18)	2024 (38)
Anticoagulants	370 (32)	2289 (43)
Thiazides/diuretics	364 (32)	1483 (28)
β-Blockers	321 (28)	2121 (40)
Calcium channel blockers	346 (30)	2527 (48)
ACE-inhibitors	369 (32)	1957 (37)
Angiotensin II receptor antagonists	261 (23)	1736 (33)
Other antihypertensives	29 (3)	462 (9)
Statins	412 (36)	2486 (47)
Glucocorticoids	146 (13)	593 (11)
Immunosuppressants	22 (2)	105 (2)
Kidney transplant recipient before index date, *n* (%)	16 (1)	337 (6)
Kidney biopsy recorded from 6 months before to 6 months after index date, *n* (%)	696 (61)	1771 (34)
Any eGFR test before index date, *n* (%)[b]	1087 (95)	5208 (99)
Days since most recent eGFR test, median (IQR)[b]	−7 (−20 to −2)	−15 (−54 to −3)
Most recent eGFR ml/min per 1.73 m^2, median (IQR)[b]	61 (34–87)	35 (17–65)

Any percentage in the table is a column percentage. NS, nephrotic syndrome; IQR, interquartile range; ACE, angiotensin-converting enzyme.

[a]During 2004–2015, only patients from Central Denmark Region and North Denmark Region were included, whereas patients from all Danish regions were included during 2016–2018.

[b]eGFR computed from plasma creatinine tests using the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2. Highest urine albumin and urine protein, and lowest plasma albumin levels from 1 month before to 1 month after first-time hospital-recorded nephrotic syndrome, and first-time recorded nephrotic proteinuria and hypoalbuminemia during 2004–2018

Characteristic	Patients with Hospital-Recorded NS	Patients with Nephrotic Proteinuria and Hypoalbuminemia
Overall, *n* (%)	1139 (100)	5268 (100)
Any proteinuria/albuminuria test ±31 d from index date, *n* (%)	842 (74)	5268 (100)
Any UACR test ±31 d from index date, *n* (%)[a]	603 (53)	3809 (72)
Days from highest recorded UACR, median (IQR)[b]	0 (−5 to 12)	0 (0–0)
Highest recorded UACR (mg/mmol), median (IQR)[b]	468 (224–736)	348 (262–527)
Any UPCR test ±31 d from index date, *n* (%)[a]	30 (3)	218 (4)
Days from highest recorded UPCR, median (IQR)[b]	1 (−2 to 23)	0 (0–3)
Highest recorded UPCR (mg/mmol), median (IQR)[b]	328 (1–634)	224 (0–472)
Any AER test ±31 d from index date, *n* (%)[a]	311 (27)	1391 (26)
Days from highest recorded AER, median (IQR)[b]	1 (0–5)	0 (−1 to 2)
Highest recorded AER (g/d), median (IQR)[b]	5.3 (3.0–8.4)	3.9 (2.7–6.0)
Any PER test ±31 d from index date, *n* (%)[a]	297 (26)	1453 (28)
Days from highest recorded PER, median (IQR)[b]	2 (−3 to 7)	0 (0–1)
Highest recorded PER (g/day), median (IQR)[b]	6.8 (4.1–10.3)	5.4 (4.0–8.4)
Any p-albumin test ±31 d from index date, *n* (%)[a]	1087 (95)	5268 (100)
Days from lowest recorded p-albumin, median (IQR)[b]	2 (−1 to 9)	0 (0–4)
Lowest recorded p-albumin (g/L), median (IQR)[b]	23 (17–30)	29 (24–32)

Any percentage in the table is a column percentage. NS, nephrotic syndrome; IQR, inter quartile range; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio; AER, urine albumin excretion rate; PER, urine protein excretion rate; p-albumin, plasma albumin.

[a]Each patient may have more than one type of proteinuria test (UACR, UPCR, AER, PER), and the highest measured level of each test was tabulated, so column numbers do not add up to 100%.

[b]Among patients with available tests ±31 days from the index date.

patients with only hospital-recorded NS were included in the laboratory databases, because 352 (93%) had an outpatient eGFR test before the index date, and 336 (89%) had a p-albumin test and 179 (47%) had a proteinuria test recorded within 31 days of the index date (Supplemental Table 2). We uncovered why 80 of these 379 patients (21%) were not included in both cohorts, as 56 patients had nephrotic proteinuria and hypoalbuminemia recorded before the study period, whereas 9 patients had nephrotic proteinuria and hypoalbuminemia recorded more than one but less than seven days apart, and 15 patients had hypoalbuminemia but with a urinary proteinuria excretion just below nephrotic range cut-off.

Discussion

We identified substantially more patients with nephrotic proteinuria and hypoalbuminemia than patients with hospital-recorded NS in Denmark during 2004–2018. At the index date, 70% of patients with nephrotic proteinuria and hypoalbuminemia had received a hospital diagnosis indicating nephropathy, whereas only 10% had received a diagnosis specific to NS. Thus, the combination of nephrotic proteinuria and hypoalbuminemia is substantially more common than the reported diagnosis of NS, and it is associated with a greater proportion of preexisting kidney disease and comorbidity, lower baseline eGFR, and more filled prescriptions of medication. Patients with hospital-recorded NS had more severe proteinuria and hypoalbuminemia, and they were more likely to have a kidney biopsy.

Similar to previous studies restricted to hospital-coded NS, this study included slightly more men than women, and participants with a large variation in age (7–10,22–24). The histopathologic findings in both our cohorts were similar to those reported in patients with NS in The Netherlands (8) and Japan (10,22). The most common findings were minimal change disease, membranous nephropathy, mesangioproliferative

Table 3. Histopathologic findings in 696 out of 1139 patients identified with first-time hospital-recorded nephrotic syndrome, and 1771 patients out of 5268 patients with first-time recorded nephrotic proteinuria and hypoalbuminemia with kidney biopsies ±6 months from the index date

Characteristic	Patients with a Kidney Biopsy in Context of Hospital-Recorded NS, *n* (%)	Patients with a Kidney Biopsy in Context of Nephrotic Proteinuria and Hypoalbuminemia, *n* (%)
Any kidney biopsy	696 (100)	1771 (100)
Any GN in kidney biopsy	668 (96)	1627 (92)
Type of GN[a]		
Minimal change disease (MCD)	185 (27)	369 (21)
Membranous nephropathy (MN)	153 (22)	236 (13)
Focal segmental glomerulosclerosis (FSGS)	77 (11)	176 (10)
Mesangioproliferative glomerulopathy	94 (14)	241 (14)
Membranoproliferative GNGN	34 (5)	69 (4)
Proliferative endocapillary GN	11 (2)	23 (1)
Deposition GN	53 (8)	85 (5)
Necrotizing and crescentic GN and vasculitis (extracapillary GN)	18 (3)	138 (8)
Diabetic nephropathy	37 (5)	102 (6)
Hypertensive nephropathy and thrombotic microangiopathies	29 (4)	134 (8)
Nonglomerular conditions (interstitial and/or tubular inflammation/ necrosis)	29 (4)	117 (7)
Other/unspecified GN and fibrosis	277 (40)	870 (49)

NS, nephrotic syndrome.
[a]Each person was allowed to contribute with more than one type of GN.

glomerulopathy, and focal segmental glomerulosclerosis, possibly reflecting that patients that underwent a biopsy in both cohorts were selected for nephrology review. Similarly to previous studies, diabetic nephropathy was rarely reported in pathology records, despite the high prevalence of diabetes in our cohorts, likely due to a reluctance to perform kidney biopsies in patients with diabetes (8–10).

Previous thromboembolic disease and use of anticoagulant drugs was more common in our cohorts (8,10,23), whereas use of antihypertensive drugs, statins, and diuretics was comparable with that in other NS cohorts (8,10,22,24). These differences likely reflect different settings and inclusion/exclusion criteria. Of note, the prevalence of diabetes and antidiabetic drug use in our patients with nephrotic proteinuria was similar to that in adults with hospital-recorded NS in Japan, but higher than that in our patients with hospital-recorded NS (10). Furthermore, the medication and laboratory profiles of patients with nephrotic proteinuria and hypoalbuminemia were comparable with American patients with diabetic kidney disease and nephrotic proteinuria (25), and Scottish patients with secondary NS (9). This suggests that the International Classification of Diseases, Tenth Revision diagnosis specific to NS is less commonly recorded in patients with NS and diabetes, and that patients with NS and diabetes, in particular, may be missed in NS cohorts based on hospital-recorded NS. Prior kidney transplantation was uncommon in our cohort with first-time hospital-recorded NS (1%), and more frequent among those with first-time nephrotic proteinuria and hypoalbuminemia (6%). Therefore, kidney transplant recipients may not receive the specific NS diagnosis code, despite having biochemistry compatible with NS.

Our findings suggest that an underlying disease may be recorded instead of NS, *e.g.*, codes reflecting diabetic nephropathy (E1x.2) or chronic GN (N03). Such alternative recording of a code potentially, but not necessarily, representing NS may be appropriate for clinical purposes. However, if the alternative recording is not random, it may lead to a lack of generalizability to all patients with NS, or information bias due to misclassification of NS in studies based on hospital diagnoses.

Our study is limited by the missing information on symptoms and clinical findings, most importantly, information on whether patients with nephrotic proteinuria and hypoalbuminemia had edema at the index date. However, the presence or absence of edema is not essential for the diagnosis of most primary conditions associated with NS (*e.g.*, minimal change disease or membranous nephropathy), and edema is often not part of the inclusion criteria in clinical trials on such conditions. Furthermore, the likelihood of edema may be influenced by other concomitant diseases, such as heart or liver diseases (1). Thus, edema may be considered a nonessential characteristic of NS, and it has previously been proposed to exclude edema from the diagnostic criteria of NS (11), leaving the biochemical criteria used in our algorithm the key criteria of NS. Yet, we must underline that we cannot verify that patients have NS solely from biochemical features, because these features may reflect other conditions (11).

Close to half of the patients in each cohort had a timed urine collection to quantify urine protein or albumin excretion rates within 31 days of the index date. Spot urine tests of albuminuria and proteinuria corrected for creatinine were commonly used to quantify proteinuria in NS, despite

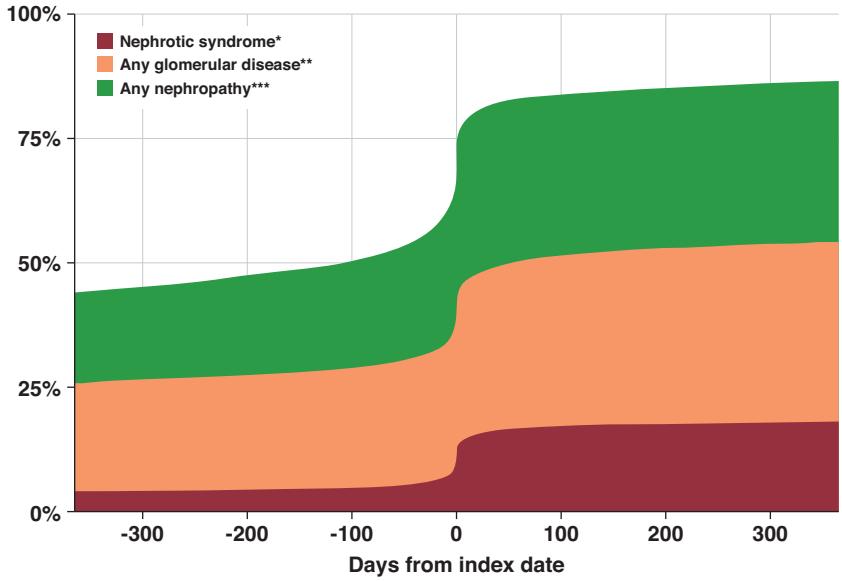

Figure 1. | Among 5268 adults with first-time nephrotic proteinuria and hypoalbuminemia, majority had diagnoses reflecting nephropathy recorded in the Danish National Patient Registry around the index date (day 0), but no more than 18% had a diagnosis specific to nephrotic syndrome after one year. Cumulative proportions of patients with kidney diseases recorded in the Danish National Patient Registry from 1 year before to 1 year after the index date (day 0) among 5268 adults with first-time nephrotic proteinuria and hypoalbuminemia during 2004–2018. *Nephrotic syndrome; **GN (including nephrotic syndrome) or diabetic nephropathy; and ***GN (including nephrotic syndrome), diabetic nephropathy, SLE, sicca (Sjögren) syndrome, glomerular diseases, renal tubulointerstitial diseases, acute kidney failure and CKD, disorder of kidney and ureter (unspecified), amyloidosis, and hypertension with nephropathy.

reported variations from the albumin and protein excretion rates, which are considered the gold standard (11,26,27). In line with current guidelines, we included both spot urine analyses and timed urine collections of both albumin and total protein to define nephrotic proteinuria (17,28) and, importantly, the fraction of patients with a timed urine sample was similar in patients identified with nephrotic proteinuria and hypoalbuminemia and in patients with a hospital-recorded NS. It should be noted that the nephrotic-range proteinuria cutoff (*i.e.*, urine protein

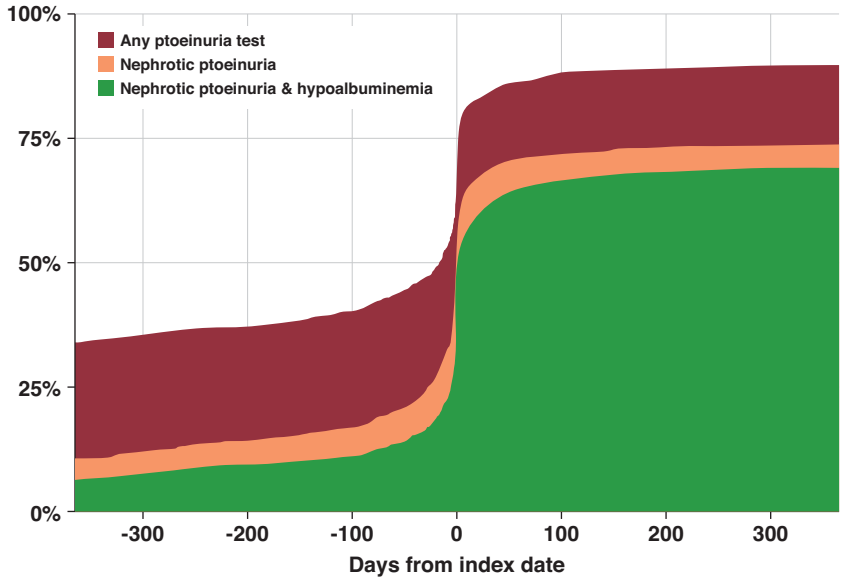

Figure 2. | Among 1139 patients with first-time hospital-recorded nephrotic syndrome, the majority had a first recording of nephrotic proteinuria and hypoalbuminemia close to the index date (day 0). Cumulative proportions of patients with any recorded proteinuria test, nephrotic proteinuria, or nephrotic proteinuria and hypoalbuminemia from 1 year before to 1 year after the index date (day 0) among 1139 patients with first-time hospital-recorded nephrotic syndrome.

excretion of 3.5 g/d) is purely arbitrary (11,17), and further analysis on alternative cutoffs may allow for the identification of additional groups of patients fitting the characteristics of NS and, thus, allow for further refinement of the definition of NS.

Finally, we uncovered why 21% of the patients with first-time hospital-recorded NS were not identified by a first-recorded nephrotic proteinuria and hypoalbuminemia during the study period. The remaining 79% may have had nephrotic proteinuria identified by bedside testing of urine (*i.e.*, not analyzed in a laboratory) or have been diagnosed with NS without confirmed laboratory tests.

In conclusion, only one fifth of patients with laboratory-recorded nephrotic proteinuria and hypoalbuminemia receive hospital diagnoses specific to NS. Compared with patients with hospital-recorded NS, those with laboratory-recorded nephrotic proteinuria and hypoalbuminemia have a higher comorbidity burden, more frequent use of medication, and considerably lower eGFR levels. This indicates that registry-based studies of patients with hospital-recorded NS only include a selected group of patients with NS. This information is essential when designing and interpreting epidemiologic studies aimed at identifying risk of and prognosis associated with NS, and it supports the use of laboratory databases to complement hospital-reported diagnoses in studies of NS.

Disclosures

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Author Contributions

H. Birn, C.F. Christiansen, A.T. Hansen, D. Nitsch, and M. Nørgaard provided supervision; H. Birn, C.F. Christiansen, and S.V. Vestergaard conceptualized the study; C.F. Christiansen, A.T. Hansen, M. Nørgaard, and S.V. Vestergaard were responsible for resources; C.F. Christiansen, D. Nitsch, and S.V. Vestergaard were responsible for formal analysis; C.F. Christiansen and S.V. Vestergaard were responsible for project administration; A.T. Hansen and S.V. Vestergaard was responsible for validation; D. Nitsch and S.V. Vestergaard were responsible for data curation; S.V. Vestergaard wrote the original draft and was responsible for funding acquisition, software, and visualization; and all authors reviewed and edited the manuscript and were responsible for investigation and methodology.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000362021/-/DCSupplemental.

Supplemental Appendix. Codebooks.

Supplemental Figure 1. Diagram of data coverage and study inclusion.

Supplemental Figure 2. Flowchart of inclusion of patients in the study.

Supplemental Figure 3. Illustration of the cohort sizes and of overlap of patients included with first-time hospital-recorded NS and first-time recorded nephrotic proteinuria and hypoalbuminemia during 2004-2018 (numbers in the circles showing the number of patients in each cohort).

Supplemental Table 1. Characteristics of patients identified with only first-time hospital-recorded NS (n= 379), only first-time nephrotic proteinuria and any hypoalbuminemia (n= 4,508), or both first-time hospital-recorded NS, and first-time recorded nephrotic proteinuria and hypoalbuminemia (n= 760) identified in Danish medical databases during 2004-2018 (any percentage is a column percentage).

Supplemental Table 2. Highest urine albumin and urine protein, and lowest plasma albumin levels from one month before to one month after index date in patients identified with only first-time hospital-recorded NS (n = 379), only first-time nephrotic proteinuria and any hypoalbuminemia (n = 4,508), or both first-time hospital-recorded NS, and first-time recorded nephrotic proteinuria and hypoalbuminemia (n = 760) identified in Danish medical databases during 2004-2018 (any percentage is a column percentage).

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