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

Søren Viborg Vestergaard,[1] Henrik Birn,[2,3] Anette Tarp Hansen,[1,4] Mette Nørgaard,[1] Dorothea Nitsch,[5] Christian Fynbo Christiansen [1]

1) Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

2) Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark

3) Department of Biomedicine, Aarhus University, Aarhus, Denmark

4) Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark

5) Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

The corresponding author's name, address, and e-mail information: Søren Viborg Vestergaard, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark, Tel.: +4587168514, Email: sovi@clin.au.dk, ORCID-id: 0000-0002-8445-7758

Key points

- Only a minority of patients with the biochemical features of 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 NS patients.

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 to adults with first-time recorded nephrotic proteinuria and hypoalbuminemia in Danish laboratory databases during 2004-2018, defining date of admission or laboratory findings as index date. We characterised these cohorts by demographics, comorbidity, medication use, and laboratory and histopathological findings.

Results

We identified 1,139 patients with hospital-recorded NS and 5,268 patients with nephrotic proteinuria and hypoalbuminemia of which 760 patients were identified with both. Within one year of the first recorded nephrotic proteinuria and hypoalbuminemia, 18% had recorded hospital diagnoses indicating the presence of NS, while 87% had diagnoses reflecting any kind of nephropathy. Among patients identified with nephrotic proteinuria and hypoalbuminemia, most recent eGFR was substantially lower (median of 35 vs.

61 ml/min/1.73 m^2), fewer underwent kidney biopsies around index date (34% vs. 61%), and prevalence of thromboembolic disease (25% vs 17%) and diabetes (39% vs. 18%) was higher when compared to 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 reveal a lower eGFR and more comorbidity. Selective and incomplete recording of NS may be an important issue when designing and interpreting studies of risks and prognosis of NS.

Introduction

Nephrotic syndrome (NS) is a clinical diagnosis defined by biochemical criteria of nephrotic proteinuria (>3.5 gram per day), hypoalbuminemia, and the presence of edema (1, 2). Data on the occurrence and prognosis of NS in adults are limited (3), and previous epidemiological 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 underlying disease is recorded instead of NS in selected groups. Therefore, it is likely that the current epidemiological findings on NS may apply only to a selected group of NS patients, and that the occurrence of NS may be underestimated. As 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, we identified patients with 1) first-time hospital-recorded NS or 2) first-time recorded nephrotic proteinuria and hypoalbuminemia in Danish medical databases in order to characterize and compare these cohorts on baseline demographics, comorbidity burden, use of medication, laboratory findings, and histopathological kidney biopsy 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 were 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) (Suppl. Figure 1).

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

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

Covariates

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

The most recent plasma creatinine measurement prior to index date was obtained to compute baseline estimated glomerular filtration rate (eGFR) (codebook 2, Appendix) using the CKD-EPI formula without correction for race (19). As 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 prior to index date (codebook 6, Appendix). To characterize the severity of NS, we identified the highest urine albumin and protein levels as well as the lowest p-albumin recorded in laboratory records from 31 days before to 31 days after the index date.

Finally, histopathological findings in kidney biopsies from six months before to six months after the index date were obtained from the National Pathology Registry (codebook 7, Appendix). (21).

Statistical analyses

We characterized patients regarding: 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 histopathological findings within six months of the index date, allowing each person to contribute with findings in more than one histopathological category.

To examine the timing of NS diagnoses in patients with hospital-recorded NS, we plotted the cumulative incidence proportions (CIPs) of first recorded proteinuria tests, first recorded nephrotic proteinuria, and first recorded nephrotic proteinuria and hypoalbuminemia from one year before to one 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 CIPs of first diagnosed NS, any glomerular disease, or any nephropathy from one year before to one year after the index date (codebook 8, Appendix).

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 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 more than one (but less than seven) days apart, or if they had a recorded hypoalbuminemia with proteinuria no more than 10% below the nephrotic range cut-off.

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 (Cary, NC, USA), and data management and analyses were conducted using R version 3.5.2.

Results

We identified 1,139 adults with first-time hospital-recorded NS and 5,268 adults with first-time nephrotic proteinuria and hypoalbuminemia, of whom 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 (Suppl. 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 to 337 (6%) of those with nephrotic proteinuria and hypoalbuminemia. Glomerulonephritis (excl. NS), chronic pulmonary disease , diabetes, and non-hematological and hematological cancer were equally common in both cohorts, but more patients with nephrotic proteinuria and hypoalbuminemia had prior acute or chronic kidney disease (37% vs. 15%), diabetes (39% vs. 18%), congestive heart failure (9% vs. 6%), or thromboembolic disease (25% vs. 17%) compared to 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 index date. The most recent eGFR was substantially lower in those with nephrotic proteinuria and hypoalbuminemia (median eGFR = 35 ml/min/1.73 m^2 [17-65]) than in those with hospital-recorded NS (median eGFR = 61 ml/min/1.73 m^2 [34-87]) (Table 1).

The highest recorded albuminuria and proteinuria levels within a month from index date were slightly higher in patients with hospital-recorded NS (e.g. median albumin-creatinine ratio = 468 mg/mmol [224-736]) than in those with nephrotic proteinuria and hypoalbuminemia (e.g. median albumin-creatinine ratio = 348 mg/mmol [262-527]). 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 p-albumin = 23 g/L [17-30]) than in those with nephrotic proteinuria and hypoalbuminemia (median p-albumin = 29 g/L [24-32]) (Table 2).

Within six 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 histopathological findings was comparable in the two cohorts, with the most common findings being minimal change disease (27% vs. 21%), ”other/unspecified glomerulonephritis and fibrosis” (40% vs. 49%), membranous nephropathy (22% vs. 13%), mesangioproliferative glomerulopathy (14% vs. 14%), and focal segmental glomerulosclerosis (11% vs. 10%) (Table 3). Of note, smaller proportions of patients with diabetes had kidney biopsies compared to other patients (43% among patients with diabetes and hospital-recorded NS and 15% among patients with diabetes and nephrotic proteinuria and hypoalbuminemia).

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

Among patients with available albuminuria or proteinuria and p-albumin tests, the majority had a 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 4,508 patients had only nephrotic proteinuria and hypoalbuminemia (Suppl. Figure 3). Patients included with only a hospital-recorded NS were comparable to those included in both cohorts with respect to age, sex, comorbidity, use of medication, and level of most recent eGFR (Suppl. Table 1). The majority of the 379 patients with only hospital-recorded NS were covered by the laboratory databases as 352 (93%) had an outpatient eGFR test before the index date, and 336 (89%) had a p-albumin and 179 (47%) had a proteinuria test recorded within 31 days of the index date (Suppl. Table 2).

We uncovered 80 of these 379 patients (21%) as prevalent characterized by nephrotic proteinuria and hypoalbuminemia recorded before the study period (n=56), as having nephrotic proteinuria and hypoalbuminemia recorded more than one but less than seven days apart (n=9), or as hypoalbuminemic but with a urinary proteinuria excretion just below nephrotic range cut-off (n=15).

Discussion

We identified substantially more patients with nephrotic proteinuria and hypoalbuminemia than patients with hospital-recorded NS in Denmark during 2004-2018. At 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 pre-existing 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, the present study included slightly more men than women, and with large variation in age (7-10, 22-24). The histopathological findings in both our cohorts were similar to those reported in patients with NS in the Netherlands (8), and Japan (10, 22), with the most common being: minimal change disease, membranous nephropathy, mesangioproliferative glomerulopathy, and focal segmental glomerulosclerosis, possibly reflecting that patients with biopsy in both cohorts were selected for nephrology review. Similarly to previous studies, diabetic nephropathy was rarely reported in pathology records despite 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 to 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 than in patients with hospital-recorded NS was similar to that in adults with hospital-recorded NS in Japan, but higher than in our patients with hospital-recorded NS (10). Furthermore, the medication and laboratory profiles of patients with nephrotic proteinuria and hypoalbuminemia were comparable to American patients with diabetic kidney disease and nephrotic proteinuria (25), and Scottish patients with secondary NS (26). This suggests that the ICD-10 diagnosis specific to NS is less commonly recorded in patients with NS and diabetes, and that especially patients with NS and diabetes 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%), thus, 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 glomerulonephritis (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 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 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 non-essential 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 as the key

criteria of NS. Yet, we must underline, that we cannot verify that patients have NS solely from the biochemical features, as these features may reflect other conditions (11).

Close to half of 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 reported variations from the albumin and protein excretion rates which are considered the gold standard (11, 27, 28). In line with the current guidelines, we included both spot urine analyses and timed urine collections of both albumin and total protein to define nephrotic proteinuria (17, 29), and importantly, the fraction of patients with a timed urine sample was similar in patients identified with nephrotic proteinuria and hypoalbuminemia and patients with a hospital-recorded NS. It should be noted that the nephrotic range proteinuria cut-off (i.e. urine protein excretion 3.5 g/day) is purely arbitrary (11, 17), and further analysis on alternative cut-offs 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 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 to 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 is essential when designing and interpreting epidemiological 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

The authors have no personal conflicts of interest to declare regarding this study. The Department of Clinical Epidemiology, The Department of Biomedicine, and the Department of Renal Medicine are involved in studies with funding from various companies as research grants to (and administered by) Aarhus University or Aarhus University Hospital. None of these studies are related to the current study. DN is on the steering group for two GlaxoSmithKline funded studies of kidney function in Sub-Saharan Africa, unrelated to the work in this paper.

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The results presented in this paper have not been published previously in whole or part, except in abstract format.

Author contributions

S Vestergaard: Conceptualization; Data curation; Formalanalysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Visualization; Writing - original draft; Writing - review and editing

H Birn: Conceptualization; Investigation; Methodology; Supervision; Writing - review and editing

A Hansen: Investigation; Methodology; Resources; Supervision; Validation; Writing - review and editing

M Nørgaard: Investigation; Methodology; Resources; Supervision; Writing - review and editing

D Nitsch: Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing - review and editing

C Christiansen: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review and editing

All authors contributed with intellectual content of critical importance to the work and approved the final version to be published.

Supplemental material

1. Codebooks
2. Supplementary figures and tables

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Tables

Table 1. Characteristics of 1,139 patients identified with first-time hospital-recorded nephrotic syndrome in the Danish National Patient Registry, and of 5,268 patients with first-time recorded nephrotic proteinuria and hypoalbuminemia identified in Danish Laboratory information systems during 2004-2018 (any percentage is a column percentage).

	Patients with hospital-recorded NS	Patients with nephrotic proteinuria and hypoalbuminemia
Overall, n (%)	1,139 (100)	5,268 (100)
Male sex, n (%)	682 (60)	3,355 (64)
Age in years, median [IQR]	60 [45, 73]	63 [50, 72]
By age group, n (%)		
18-49 years	361 (32)	1,329 (25)
50-64 years	310 (27)	1,646 (31)
65+ years	468 (41)	2,293 (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)	3,041 (58)
Hospital-recorded kidney disease during 10 years prior to index date, n (%)		
Glomerulonephritis (excl. nephrotic syndrome)	109 (10)	538 (10)
Renal tubulointerstitial diseases	41 (4)	391 (7)
Acute kidney injury and or chronic kidney disease	166 (15)	1,930 (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 years prior to index date, n (%)		
Diabetes	206 (18)	2,032 (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)	1,328 (25)
Non-hematological cancer (excl. non-melanoma skin cancer)	89 (8)	485 (9)
Hematological cancer	42 (4)	149 (3)
Filled prescriptions within 365 days prior to index date, n (%)		
Antidiabetics, n (%)	203 (18)	2,024 (38)
Anticoagulants, n (%)	370 (32)	2,289 (43)
Thiazides/diuretics, n (%)	364 (32)	1,483 (28)
Beta blockers, n (%)	321 (28)	2,121 (40)
Calcium channel blockers, n (%)	346 (30)	2,527 (48)
ACE-inhibitors, n (%)	369 (32)	1,957 (37)

Angiotensin-II receptor antagonists, n (%)	261 (23)	1,736 (33)
Other antihypertensives, n (%)	29 (3)	462 (9)
Statins, n (%)	412 (36)	2,486 (47)
Glucocorticoids	146 (13)	593 (11)
Immunosuppressants	22 (2)	105 (2)
Kidney transplant recipient prior to index date, n (%)	16 (1)	337 (6)
Kidney biopsy recorded from six months before to six months after index date, n (%)	696 (61)	1,771 (34)
Any eGFR test before index date, n (%) [b]	1,087 (95)	5,208 (99)
Days since most recent eGFR test, median [IQR] [b]	-7 [-20, -2]	-15 [-54, -3]
Most recent eGFR ml/min/1.73 m^2, median [IQR] [b]	61 [34, 87]	35 [17, 65]

NS, nephrotic syndrome; IQR, inter quartile range; ACE-inhibitors, Angiotensin-converting enzyme inhibitors; eGFR, estimated glomerular filtration rate

[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 CKD-EPI formula

Table 2. Highest urine albumin and urine protein, and lowest plasma albumin levels from one month before to one month after first-time hospital-recorded nephrotic syndrome, and first-time recorded nephrotic proteinuria and hypoalbuminemia during 2004-2018 (any percentage is a column percentage).

	Patients with hospital-recorded NS	Patients with nephrotic proteinuria and hypoalbuminemia
Overall, n (%)	1,139 (100)	5,268 (100)
Any proteinuria/albuminuria test +/- 31 days from index date, n (%)	842 (74)	5,268 (100)
Any UACR test +/- 31 days from index date, n (%) [a]	603 (53)	3,809 (72)
Days from highest recorded UACR, median [IQR] [b]	0 [-5, 12]	0 [0, 0]
Highest recorded UACR mg/mmol, median [IQR] [b]	468 [224, 736]	348 [262, 527]
Any UPCR test +/- 31 days from index date, n (%) [a]	30 (3)	218 (4)
Days from highest recorded UPCR, median [IQR] [b]	1 [-2, 23]	0 [0, 3]
Highest recorded UPCR mg/mmol, median [IQR] [b]	328 [1, 634]	224 [0, 472]
Any AER test +/- 31 days from index date, n (%) [a]	311 (27)	1,391 (26)
Days from highest recorded AER, median [IQR] [b]	1 [0, 5]	0 [-1, 2]
Highest recorded AER g/day, median [IQR] [b]	5.3 [3.0, 8.4]	3.9 [2.7, 6.0]
Any PER test +/- 31 days from index date, n (%) [a]	297 (26)	1,453 (28)
Days from highest recorded PER, median [IQR] [b]	2 [-3, 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 days from index date, n (%) [a]	1,087 (95)	5,268 (100)
Days from lowest recorded p-albumin, median [IQR] [b]	2 [-1, 9]	0 [0, 4]
Lowest recorded p-albumin g/L, median [IQR] [b]	23 [17, 30]	29 [24, 32]

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 a hundred percent.

[b] Among patients with available tests +/- 31 days from index date

Table 3. Histopathological findings in 696 out of 1,139 patients identified with first-time hospital-recorded nephrotic syndrome, and 1,771 patients out of 5,268 patients with first-time recorded nephrotic proteinuria and hypoalbuminemia with kidney biopsies +/- six months from the index date.

	Patients with a kidney biopsy in context of hospital-recorded NS	Patients with a kidney biopsy in context of nephrotic proteinuria and hypoalbuminemia
	n (%)	n (%)
Any kidney biopsy	696 (100)	1,771 (100)
Any glomerulonephritis in kidney biopsy	668 (96)	1,627 (92)
Type of glomerulonephritis[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 (MesPGN)	94 (14)	241 (14)
Membranoproliferative glomerulonephritis	34 (5)	69 (4)
Proliferative endocapillary glomerulonephritis	11 (2)	23 (1)
Deposition glomerulonephritis	53 (8)	85 (5)
Necrotizing and crescentic glomerulonephritis and vasculitis (extracapillary glomerulonephritis)	18 (3)	138 (8)
Diabetic nephropathy	37 (5)	102 (6)
Hypertensive nephropathy and thrombotic microangiopathies	29 (4)	134 (8)
Non-glomerular conditions (interstitial and/or tubular inflammation/necrosis)	29 (4)	117 (7)
Other/unspecified glomerulonephritis and fibrosis (GN UNS)	277 (40)	870 (49)

[a] Each person was allowed to contribute with more than one type of glomerulonephritis

Figure legends

Figure 1. Cumulative proportions of patients with kidney diseases recorded in the Danish National Patient Registry from one year before to one year after the index date (day 0) among 5,268 adults with first-time nephrotic proteinuria and hypoalbuminemia during 2004-2018.

* Nephrotic Syndrome

** Glomerulonephritis (incl. nephrotic syndrome) or diabetic nephropathy

*** Glomerulonephritis (incl. nephrotic syndrome), diabetic nephropathy, systemic lupus erythematosus (SLE), sicca syndrome [Sjögren], glomerular diseases, renal tubulointerstitial diseases, acute kidney failure and chronic kidney disease, disorder of kidney and ureter (unspecified), amyloidosis, hypertension with nephropathy

Figure 2. Cumulative proportions of patients with any recorded proteinuria test, nephrotic proteinuria, or nephrotic proteinuria and hypoalbuminemia from one year before to one year after the index date (day 0) among 1,139 patients with first-time hospital-recorded nephrotic syndrome.

Figure 1

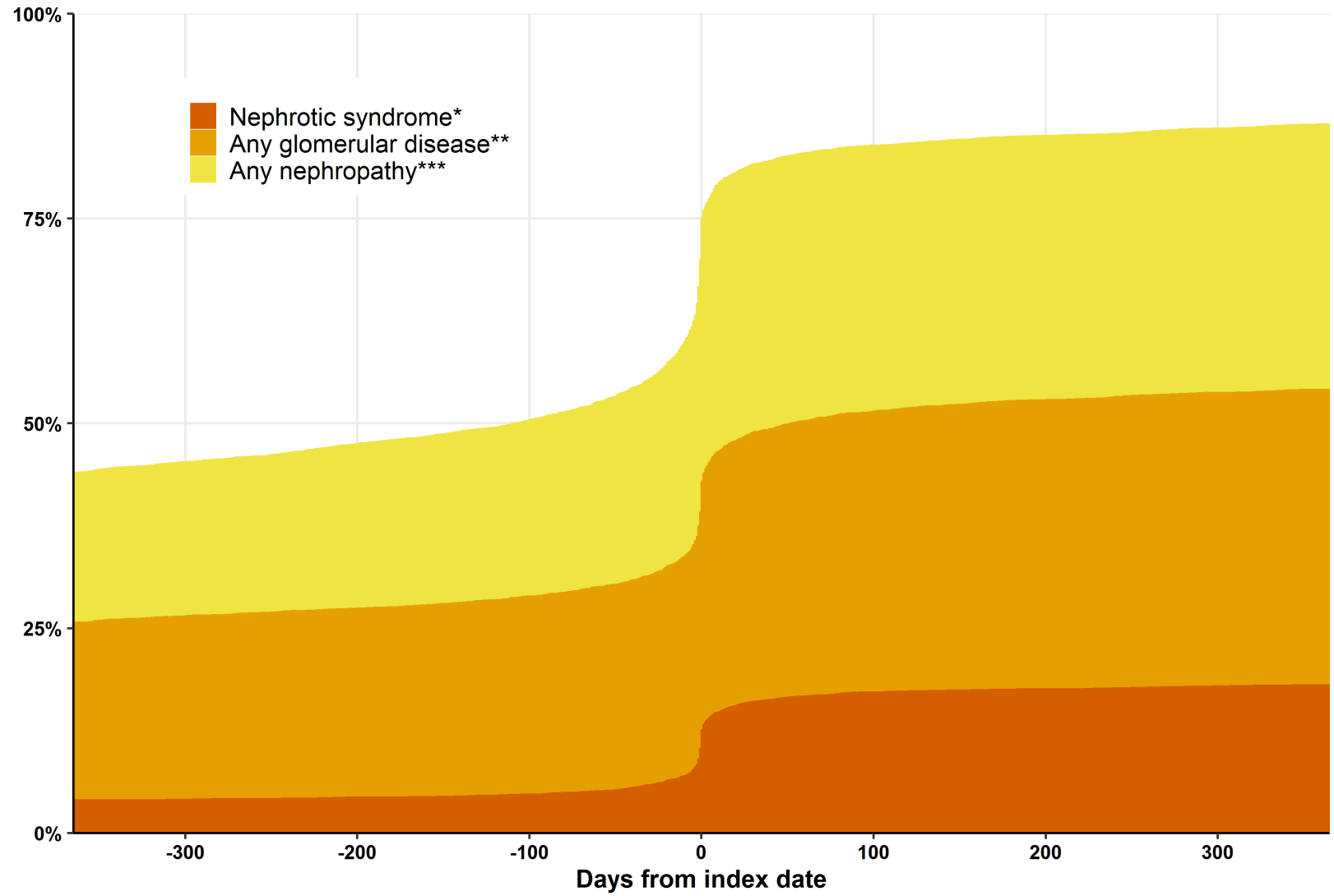
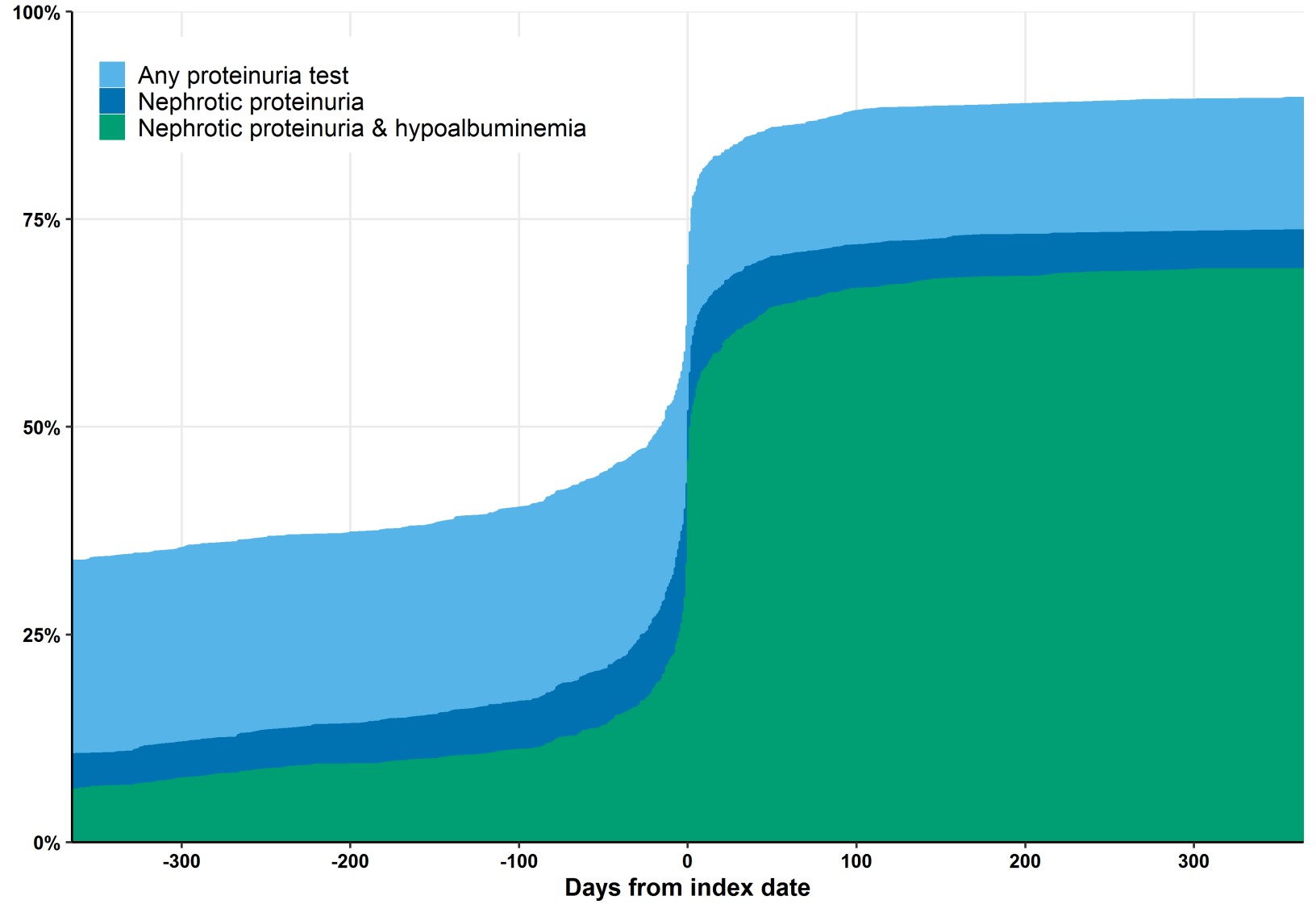

100%
75%
50%
25%
0%
Nephrotic syndrome*
Any glomerular disease**
Any nephropathy***
-300
-200
-100
0
100
200
300
Days from index date

Figure 2


100%
75%
50%
25%
0%
Any proteinuria test
Nephrotic proteinuria
Nephrotic proteinuria & hypoalbuminemia
-300
-200
-100
0
100
200
300
Days from index date