Proteinuria in COVID-19: prevalence, characterization and prognostic role

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Abstract

**Background:** Proteinuria has been commonly reported in patients with COVID-19, suggesting a renal involvement in this infection. However, only dipstick tests have been used thus far. Here, the quantification and characterization of proteinuria and hematuria are investigated. Their potential association with mortality was assessed.

**Methods:** This retrospective, observational and monocentric study includes 153 patients hospitalized with COVID-19 between March 28th and April 30th 2020, in whom total proteinuria and urine α₁-microglobulin (a marker of tubular injury) have been measured. Association with mortality was evaluated with a follow-up until May 7th 2020.

**Results:** According to the Kidney Disease Improving Global Outcomes staging, 14% (n=21) had stage 1 proteinuria (<150 mg/g of urine creatinine), 42% (n=64) had stage 2 (between 150 and 500 mg/g) and 44% (n=68) had stage 3 (over 500 mg/g). Urine α₁-microglobulin concentration was higher than 10 or 15 mg/g in 94% and 89% of patients, respectively. After a median follow-up of 27 [14;30] days, the mortality rate reached 18%. Total proteinuria and urine α₁-microglobulin (as continuous and/or categorical variables) were associated with mortality in unadjusted and adjusted models. This association was even stronger in subgroups of patients with normal renal function or without urinary catheter.

**Conclusions:** Proteinuria is frequent in patients with COVID-19. Its characterization suggests a tubular origin with increased urine α₁-microglobulin. Tubular proteinuria seems associated with mortality in COVID-19.

Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes « coronavirus disease 2019 » (COVID-19) [1,2] which is characterized by diffuse alveolar damage leading to an acute respiratory distress syndrome [3]. Other organs may also be affected [2–4]. Cheng et al. [2] early described a high prevalence of proteinuria (43.9%) and hematuria (26.7%) in a cohort of 442 patients in Wuhan, China [2]. These data suggest a specific kidney damage caused by SARS-CoV-2, although it remains unclear whether the virus is present in the urine or not [5,6]. Since this first publication, measurement of proteinuria was recommended in our institution. Contrary to the pilot reports based on dipstick tests (with well-established limitations [7]), quantitative measurements and characterization of proteinuria were performed. In the present paper, we aim at characterizing the prevalence and type of proteinuria observed in patients with COVID-19, and we assess the prognostic yield of proteinuria in COVID-19.

Methods

**Patients and methods**
This is an observational retrospective single-center study. Clinical and biological variables were extracted from the computer-based medical records. All data were anonymized and the study had been approved by the Ethics Committee of ULiège Academic Hospital.

**Inclusion criteria.** All patients older than 18 years admitted to Liège Academic Hospital between March 28th and April 30th 2020 with a positive COVID-19 test (reverse transcriptase polymerase chain reaction (RT-PCR, Cobas SARS CoV-2 Test with Cobas 8800) via nasal swab or antigen testing) were eligible (only one has positive antigen without RT-PCR). Analysis was only considered in patients with at least one complete urine analysis (red blood cells (RBC) count, total proteinuria and α₁-microglobulin). Quantification of urinary β₂-microglobulin was available in a subset of patients. Patients suffering from end-stage renal disease (i.e. renal transplantation or chronic dialysis) were excluded.

**Urine samples.** The day when the urine was collected was considered as Day 0 (D0). A second urine analysis was performed in some patients on Day 7 (D7). Total proteinuria (expressed in mg/g of urine creatinine) was measured on a random spot with Abbott Alinity instrument whereas urine α₁-microglobulin and β₂-microglobulin were determined on the Siemens Dimension Vista instrument. Proteinuria was staged according to the KDIGO (Kidney Disease Improving Global Outcomes) staging system [8]: normal or stage 1 (<150 mg/g), stage 2 (between 150 and 500 mg/g), stage 3 (over 500 mg/g). Urine α₁-microglobulin was expressed in mg/g of urine creatinine. Tertiles and two different thresholds were considered (>10 or >15 mg/g [9,10]). Urine β₂-microglobulin was expressed in mg/L. Tertiles and a result above 0.19 mg/L was considered as abnormal [11]. The number of RBC in the urine was automatically evaluated by the Sedimix automate (positive if 5 RBC per field). Because proteinuria and hematuria can be impacted by urinary catheter (UC), analyses were repeated in subgroups without UC at D0.

**Clinical, biological and radiological parameters.**

The following variables were considered: age, weight, height, body mass index (BMI), history of hypertension (based on medical records and/or the presence of antihypertensive medications at admission), history of diabetes (based on medical records and/or the presence of specific therapy at admission), active cancer, active smoking, and history of CKD (based on medical records, not on biological data). Biological data of interest were considered at the closest time of measurement to D0 within a maximum of 48 hours. All biological data were generated from one single laboratory (Unilab, CHU de Liège) accredited for ISO 15189 Guideline. The following variables were collected: C-reactive protein (CRP), procalcitonin, serum creatinine, lactate dehydrogenase (LDH), albumin, sodium, potassium, total calcium, bicarbonates concentrations (Abbott Alinity instrument), leucocytes, lymphocytes, platelet counts, hemoglobin (Sysmex SE-9000 Hematology analyzer), and D-Dimer (Innovance D-Dimer kit on the Siemens CS5100 automate).

A clear distinction between chronic kidney disease (CKD) and acute kidney injury (AKI) is not always possible. Therefore, we used the term “decreased kidney function”, based on the CKD-Epidemiology
equation and using an age-calibrated definition: estimated glomerular filtration rate (eGFR) below 75, 60 or 45 mL/min/1.73m² for patients younger than 40 years, between 40 and 65 years or older than 65 years, respectively [12,13]. Because proteinuria and hematuria can be influenced by CKD status and/or AKI, analyses were repeated in subgroups without decreased eGFR at D0.

A thorax CT-scanner staging was used to assess the radiographic severity of COVID-19 pneumonia (percentage of the lungs involved) as reported by radiologists in medical records (except for two patients): <10%, between 10 and 50%, and > 50%.

Severe cases on D0 were defined according to the guidelines of the Chinese National Health Commission: (i) respiratory rate >30 breaths/min, (ii) oxygen saturation <93%, or (iii) PaO₂/FiO₂ ratio ≥300 mmHg [2].

Mortality status was checked for all patients in the medical records and confirmed by a phone call to general practitioners until May 7th 2020.

Statistical analyses

Data are expressed as mean ± standard deviation (SD) when the distribution was normal and as median with quartiles when not. Normality was assessed by the Shapiro-Wilk test. Comparison of two independent groups were performed using Mann-Whitney U test or Chi-square test for continuous and categorical variables respectively. Kruskal-Wallis test with post-hoc test according to Dunn and exact Chi² test (with Bonferroni correction) were performed to compare more than two groups for continuous variables and categorical variables, respectively. Univariate survival analysis (Kaplan-Meier) was done with categorical urine variables (according to KDIGO for proteinuria, to tertiles for urine α₁-microglobulin and β₂-microglobulin, and more than 10 RBC per field for hematuria) as strata. Cox proportional hazard regression modelling using the backward selection procedure was performed to study the risk of mortality associated with all variables in Table 1. Proteinuria, urine α₁-microglobulin and hematuria considered as a categorical or continuous variable, were studied in non-adjusted models and adjusted for other covariates at D0 that were significant in the unadjusted model. All statistics were performed with MedCalc statistical software (Medcalc, Mariakerke, Belgium).

Results

Characteristics of the population

The final cohort included 153 patients (flowchart of patients’ inclusion in Figure S1). The median time period between admission and D0 was 3 [2;5] days. The patients excluded from the analysis because of the lack of urine samples (n=72) were more frequently women and had a higher and earlier mortality rate (Table S1). The median age of our cohort was 70 [58-81] years old, and 39% were women (Table 1). COVID-19 patients were characterized by high serum CRP and LDH concentrations and low lymphocyte number (Table 1). Eighty-two % of patients were staged as severe pneumonia. Twenty-three (15%)
patients died during the hospitalization and 4 deaths occurred after the patient left the hospital leading to a mortality rate of 18% during the study period. At the end of the follow-up, 17 were still hospitalized.

Renal parameters

On D0, serum creatinine concentration was higher than normal in 27% of patients. A decreased renal function on D0 was observed in 24% of patients.

Proteinuria

The median proteinuria in our 153-patient cohort was 455 [238;834] mg/g at D0. Fourteen percent (n=21) had stage 1 proteinuria, 42% (n=64) had stage 2 and 44% (n=68) had stage 3. Two patients had heavy proteinuria (over 3500 mg/g). Clinical and biological characteristics according to proteinuria stages are shown in Table S2. Among the 153 patients, a pre-admission value of proteinuria was available for 51 patients within a median preceding time of 383 [161;836] days. Among the 32 patients with prior abnormal proteinuria, only 2 had normal proteinuria at D0. Conversely, among the 19 patients with prior normal proteinuria, only 4 remained within the normal range during the study period. One of the two patients with heavy proteinuria during COVID-19 had a normal proteinuria documented 57 days before D0. Limiting analysis to 112 patients with less than 10 RBC per field, abnormal proteinuria was still found in 81% of patients. Among the 114 patients without UC, 82% had proteinuria (38% with stage 3). Among the 122 patients without decreased eGFR on D0, 83% had abnormal proteinuria (43% with stage 3).

The median urinary concentrations of α₁-microglobulin and β₂-microglobulin (n=94) were 54 [27;122] mg/g and 2.65 [0.40;14.15] mg/L, respectively. α₁-microglobulin concentration was higher than 10 and 15 mg/g in 94% and 89% of patients, respectively. Urine β₂-microglobulin was higher than 0.19 mg/L in 85% of patients. Among the 114 patients without UC, urine α₁-microglobulin over 15 mg/g and urine β₂-microglobulin over 0.19 mg/L were found in 86% and 84%, respectively. Among the 122 patients without decreased eGFR on D0, 87% and 83% had α₁-microglobulin and β₂-microglobulin concentrations over 15 mg/g and 0.19 mg/L, respectively.

Table 2 describes the clinical and biological characteristics of the patients according to tertiles of urine α₁-microglobulin and Table S3 describes the clinical and biological characteristics of the patients according to tertiles of urine β₂-microglobulin.

Hematuria

The incidence of hematuria in the 153-patient cohort was 36% and 26% if the threshold of 5 or 10 RBC per field was considered, respectively. In patients without UC (n=114), the prevalence of hematuria (>10 RBC per field) was 13%.

Factors at D0 associated with mortality
Mortality was assessed for all patients on May 7th 2020 with a median follow-up of 27 [14;30] days, D0 being the reference date. During the follow-up, 27 patients died (18%). The median time period between D0 and date of death was 7 [4;12] days.

Comparison of variables at D0 between patients who died versus survived is shown in Table S4. The patients who died were older, more frequently men and had more frequently a history of CKD and known active cancer. They had lower eGFR, lower platelet counts and higher CRP concentrations. For urine parameters, proteinuria, urine α₁-microglobulin, urine β₂-microglobulin, number of RBC per field and UC were also significantly higher in deceased patients. Urine analyses were also performed in sub-groups and showed similar results (Table S5).

In univariate Cox proportional hazards regression analysis, the following parameters were associated with mortality: age (HR 1.03 95% CI: 1.00-1.06, p=0.03), male gender (HR 2.94 95% CI: 1.22-7.69, p=0.02), history of CKD (HR 2.35 95% CI: 1.03-5.38, p=0.04), active cancer (HR 2.95 95% CI: 1.19-7.34, p=0.02), eGFR (for 10 unit decrease: HR 1.16 95% CI: 1.01-1.34, p=0.03), CRP (for 10 unit increase: HR 1.04 95% CI: 1.00-1.08, p=0.04), platelet counts (for 10,000 unit decrease: HR 1.01 95% CI: 1.00-1.01, p=0.004), stage 3 proteinuria (versus stage 2: HR 2.83 95% CI: 1.19-6.72, p=0.02), urine α₁-microglobulin as a continuous variable (for 10 unit increase: HR 1.03 95% CI: 1.01-1.05, p=0.004) or categorical variable (tertiles 3 versus 1: HR 5.41 95% CI: 1.83-16.00, p=0.002 and tertiles 3 versus 2: HR 4.40 95% CI: 1.63-11.90, p=0.004), hematuria (HR 2.82 95% CI: 1.32-6.01, p=0.007) and bladder catheterization (HR 4.18 95% CI: 1.95-8.95, p=0.0002). Kaplan Meier survival curves for proteinuria stages, urine α₁-microglobulin tertiles and hematuria (RBC more than 10 per field) as strata are shown in Figure 1. High tertiles of proteinuria and urine α₁-microglobulin and hematuria were associated with lower survival (logrank test, p=0.008, 0.0001 and 0.005, respectively). Focusing on urine variables, multivariable Cox adjusted analyses are shown in Table 3 for categorical variables and in Table S6 for continuous ones. Urine α₁-microglobulin (when considered as a categorical variable) was still associated with mortality in the adjusted models, except when the variable UC was included. Hematuria as a continuous variable was not associated with mortality (data not shown) but well as a categorical variable in the adjusted models. However, such association was not observed in the subgroup of patients without UC. The presence of UC was highly predictive of mortality in all models. In patients with normal eGFR on D0, proteinuria (as a continuous and a categorical variable) and urine α₁-microglobulin (as a categorical variable) were still associated with mortality in the full-adjusted model. The same results were observed in the sub-group without UC at D0. Forcing variables like score severity and hospitalization in ICU at D0 in the Cox models did not modify the results.

Follow-up results at day 7

Among the 153 patients, 76 left the hospital less than 7 days after D0. Among the 77 patients still hospitalized at D7, 48 had a second measurement of proteinuria. Among them, the median concentration of proteinuria and urine α₁-microglobulin at D0 was 493 [307;929] mg/g and 76 [37;144] mg/g, and 280
[170;521] mg/g and 60 [34;125] mg/g at D7, respectively. The median decrease in proteinuria and α₁-microglobulin concentration was -178 [-531;-52] mg/g (relative decrease of 43%) and -17 [-56;32] mg/g (relative decrease of 21%), respectively. Excluding the patients who died during the study period (n=8) and those who were still hospitalized on May 7th (n=6), it leaves 34 patients who left the hospital alive with a median concentration of proteinuria and α₁-microglobulin on D0 of 483 [302;1062] mg/g and 60 [33;138] mg/g, and of 203 [109;328] mg/g and 34 [14;84] mg/g on D7, respectively. The median decrease in proteinuria and α₁-microglobulin concentration was -256 [-717;-98] mg/g (relative decrease of 58%) and -20 [-91;-3] mg/g (relative decrease of 43%), respectively. Among these patients, proteinuria stage 1, 2 and 3 was observed in 9%, 44% and 47% respectively on D0. The prevalence was 32%, 50% and 18%, respectively on D7. Among the 3 patients with stage 1 on D0, 2 progressed to stage 2 at D7. Among the 15 patients with stage 2 on D0, 8 decreased to stage 1, one progressed to stage 3 and 6 remained at stage 2 on D7. Among the 16 patients with stage 3 on D0, 2 decreased to stage 1, 9 to stage 2 and 5 remained at stage 3 on day 7.

**Discussion**

In the current retrospective analysis of a cohort of 153 hospitalized patients with COVID-19, we found a high prevalence (close to 80%) of patients with abnormal proteinuria (including 43% of them with stage 3 proteinuria). The characterization of the proteinuria showed a predominant rate of tubular proteinuria, as depicted by urine α₁-microglobulin and β₂-microglobulin measurements. Ninety-four % of patients had increased α₁-microglobulin values. Interestingly, total proteinuria and α₁-microglobulin concentrations were predictive of mortality in our cohort.

The high prevalence of proteinuria in patients with COVID-19 is not related to hematuria. Indeed, excluding patients with hematuria (26%), abnormal proteinuria was still found in 81% of cases. Whether the proteinuria is directly caused by the SARS-CoV-2 cannot be proven due to the retrospective design of our study. However, pre-admission values of proteinuria were available for 51 patients and only 4 out of 19 patients who had prior normal proteinuria also had normal values at D0. This is suggesting de novo proteinuria due to COVID-19. Cheng et al. [2] observed proteinuria in 43.9% of patients COVID-19. The same group in another publication observed proteinuria in 65.8% of 333 hospitalized patients [14]. Hirsch et al [15] found a prevalence of 42.1%, by dipstick results, in 646 patients in New-York City.

To the best of our knowledge, this is the first study that characterizes and quantifies the proteinuria of patients hospitalized with COVID-19. The fact that we measured proteinuria instead of dipsticks may per se explain the higher prevalence of positive results in our cohort, especially because dipstick is more sensitive for albuminuria than for tubular proteinuria [7]. Our analysis revealed that proteinuria is mostly from tubular origin. The underlying mechanisms remain unknown. The design of the current study did not allow us to formally distinguish acute tubular necrosis (ATN) caused by septic condition or low-oxygen delivery to tissues from specific cytopathic lesions caused by the SARS-CoV-2 itself [16]. Some preliminary results with kidney biopsies (including electronic microscopy) suggested a direct virus-
mediated tubular injury [17–19]. This hypothesis is reinforced by the preferential tubular expression of
the angiotensin converting enzyme 2 which is suspected to participate in cellular entry of the SARS-CoV-2
[4,20,21]. However, the presence of the virus in the kidney (and in urine) is still subject of active debate
and further studies are needed [17–19,21–23]. In our study, it is interesting to note that there were much
more patients with isolated proteinuria than patients with decreased eGFR at admission (20% at D0).
Only a small part of patients were hospitalized in intensive care at D0. During the hospitalization (and
until May 7th), the incidence of AKI (defined according to the creatinine criteria of the KDIGO [24] after D0)
occurred in 23 patients (15%), once again a much lower prevalence than abnormal proteinuria. These
observations rather suggest a direct viral impact on the renal tubules than ATN secondary to host
systemic inflammation in response to the viral infection.

Fifteen percent of patients died during the hospitalization, a prevalence comparable to data available in
New York City [25], Northern Italy [26], or China [2]. Parameters at D0 associated with mortality in our
cohort (age, sex, history of CKD, active cancer, lower eGFR and platelet counts, and higher CRP) have
already been reported by others [27,28]. Interestingly, proteinuria and even more urine α₁-microglobulin
seem to be associated with mortality. UC was highly predictive of mortality, probably as a mixed reflection
of frailty of the patient and/or severity of the disease. Because UC can cause hematuria by itself and thus
“false” proteinuria, it is legitimate to discard patients with UC at D0 from the survival analysis. In the sub-
group without UC, the predictive value of proteinuria and urine α₁-microglobulin was confirmed.
Hematuria was not predictive per se. Cheng et al. [2] also found an association between kidney
involvement, including proteinuria (by dipstick), and in-hospital death. Once again, the design of our study
only allows to generate hypotheses to explain the higher mortality rate in patients with abnormal
proteinuria (higher viral load and early multiple organ involvement [16,29] or marker of ATN).

The long-term renal consequences of COVID-19 are still unknown and will require follow-up studies. Pei et
al. [14] have observed that proteinuria often resolved (in 68.5% of the patients with prior proteinuria)
within 3 weeks. Our preliminary data seem reassuring, but more distant follow-up of the proteinuria is
needed.

The study has limitations. First, the study is monocentric and retrospective. Second, all analyses were
performed on D0, which was defined by the time of urine analysis. A median period of 3 days separates
admission, and D0 and our results must be interpreted accordingly. Significant differences between
included and non-included patients (Table S1) are observed essentially in terms of mortality and time to
death. This bias is mainly due to a lack of urine collection in severely ill patients who died rapidly after
their admission. The analyses concerning mortality rate should also be considered with caution because
of the small sample size. Tubular involvement suggested in our study does not exclude more exceptional
forms of glomerular involvement like collapsing glomerulopathy [30]. Data about urinary albumin were
not available (not reimbursed by the Belgian health system) and mixed proteinuria cannot be excluded.
Lastly, variables like weight and height were not available in some patients.
In conclusion, a very high rate of tubular proteinuria is found in hospitalized COVID-19 patients. Proteinuria and/or urine α₁-microglobulin were associated with mortality, even in adjusted models. This is especially relevant in patients with normal eGFR at D0 and patients without UC.

**Declarations**

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**Ethics approval:** The Ethics Committee of ULiège Academic Hospital approved the study and waived the requirement to obtain informed consent based on the observational design.

**Consent to participate:** not applicable.

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**Availability of data and material:** the data underlying this article will be shared on reasonable request to the corresponding author.

**Code availability:** not applicable.

**Authors’ Contributions:**

Design the study: JH, AB, FJ, PD

Collect clinical data: JH, AB, PE, SG, GR, PW, CB, JMK, MT, BL, BM, FJ, PD

Perform biological analyses: LL, EC

Design and perform statistical analyses: JH, AB, MT, HP, CM, SB, FJ, PD

Draft the initial version manuscript: JH, AB, JMK, HP, FJ, PD

Revise the manuscript critically for intellectual content: LL, PE, SG, GR, PW, CB, BL, BM, CM, EC, SB

All authors read and approved the final manuscript.

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Tables

Table 1: Clinical and biological characteristics of the cohort at D0
| CLINICAL                      |                  |
|------------------------------|------------------|
| Age (years) (n=153)          |                  |
| <40 years (%)                | 70 [58;81]       |
| [40-65] years                | 35               |
| >65 years (%)                | 59               |
| Women (n=153) (%)            | 39               |
| Weight (n=130) (kg)          | 80±17            |
| Height (n=125) (m)           | 1.70 [1.62;1.78] |
| Body Mass index (n=120) (kg/m²) |            |
| <18.5 (%)                    | 28 [24;31]       |
| [18.5-25] (%)                | 3                |
| [25-30] (%)                  | 27               |
| ≥30 (%)                      | 43               |
| Medical history (n=153)      |                  |
| Hypertension (%)             | 59               |
| Diabetes (%)                 | 43               |
| Chronic kidney disease (%)   | 17               |
| Active cancer (%)            | 10               |
| Active smoking (%)           | 5                |
| Intensive Care Unit (%)      | 22               |
| Severe case (%)              | 82               |
| Thoracic CT-Scanner staging (n=151) (%) |           |
| Normal                       | 17               |
| Minor (<10%)                 | 7                |
| Mild (10-50%)                | 61               |
| Severe (>50%)                | 16               |
| BIOLOGICAL (D0)              |                  |
| C-reactive protein (n=153) (mg/L) | 81 [38;155]   |
| C-reactive protein>5 mg/L    | 97%              |
| Procalcitonin (n=143) (µg/L) |                  |
| Procalcitonin <0.05 (%)      | 0.14 [0.07;0.34] |
| Procalcitonin [0.05-0.5] (%) | 10               |
| Procalcitonin [0.5-2] (%)    | 73               |
| Procalcitonin [2-10] (%)     | 10               |
| Procalcitonin ≥10 (%)        | 3                |
| Leucocytes (n=153) (/mm³)    |                  |
| >10100/mm³ (%)               | 6180 [4650;9060] |
| <4600/mm³ (%)                | 19               |
| Lymphocytes (n=151) (/mm³)   | 860 [655;1155]   |
| Hemoglobin (n=153) (g/dL)    | 12.3 [11.2;13.6] |
| Platelet (n=153) (x1000/mm³) | 230 [165;301]   |
| Lactate Dehydrogenase (n=153) (U/L) | 342 [259;443] |
| >220 (%)                     | 87               |
| D-Dimer (n=141) (µg/L)       |                  |
| >500 (%)                     | 1009 [715;1878]  |
| Albumin (n=148) (g/L)        |                  |
| <32 (%)                      | 34±5             |
| Potassium (n=153) (mmol/L)   |                  |
| >5.1 (%)                     | 4.10±0.47        |
| <2.5 (%) | 9 |
|---|---|
| Sodium (n=153) (mmol/L) | 139 [137;142] |
| <136 (%) | 14 |
| Calcium (n=153) (mmol/L) | 2.10 [2.01;2.20] |
| <2.2 (%) | 72 |
| Bicarbonates (n=145) (mmol/L) | 25.5 [23.1;27.6] |
| <22.1 (%) | 17 |
| >31 (%) | 7 |

Table 2: Clinical and biological characteristics of the patients at D0 according to tertiles of urinary α₁-microglobulin at D0
### Tertile 1

- Less than or equal to 32 mg/g (n=51)

### Tertile 2

- 32-86 mg/g (n=50)

### Tertile 3

- Greater than 86 mg/g (n=52)

#### Kruskal Wallis test (or exact Chi-square test)

| Variable                                      | Tertile 1       | Tertile 2       | Tertile 3       | P-value          |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| AL                                            | 66 [57;80]*     | 65 [58;73]*     | 77 [70;85]      | 0.005           |
| (%)                                           | 49              | 34              | 33              | ns              |
| (kg)                                          | 79 [65;94]      | 83 [69;93]      | 75 [68;90]      | ns              |
| (m)                                           | 1.68 [1.61;1.79] | 1.74 [1.67;1.79] | 1.70 [1.65;1.76] | ns              |
| Ass index (kg/m²)                             | 28 [25;31]      | 28 [23;30]      | 27 [23;29]      | ns              |
| History                                       |                 |                 |                 |                 |
| Hypertension (%)                              | 57              | 62              | 58              | ns              |
| DM (%)                                        | 29              | 18              | 37              | ns              |
| CVD (%)                                       | 4*              | 8*              | 38              | <0.0001         |
| Cancer (%)                                    | 8               | 10              | 6               | ns              |
| Smoking (%)                                   | 6               | 2               | 13              | ns              |
| ICU (%)                                       | 14              | 24              | 27              | ns              |
| Cases (%)                                     | 69*             | 86              | 90              | 0.004           |
| **CICAL**                                    |                 |                 |                 |                 |
| AL (D0) (mg/dL)                               | 0.87 [0.70;0.99]* | 0.91 [0.76;1.06] | 1.04 [0.86;1.49] | 0.007           |
| mL/min/1.73 m²                                | 82 [61;95]*     | 82 [61;93]*     | 61 [45;83]      | 0.002           |
| Urine protein (mg/dL)                         | 61 [15;108]     | 135 [54;216]$^*$ | 95 [47;147]$^*$ | 0.0001          |
| Uric acid (µg/L)                              | 0.08 [0.05;0.15] | 0.16 [0.08;0.46]$^*$ | 0.28 [0.09;0.42]$^*$ | 0.0004          |
| Yt:es count (/mll)                            | 5940 [4260;5940] | 6720 [5170;10100] | 6110 [4630;8615] | ns              |
| Yt:es count (/mmll)                           | 925 [720;1350]  | 850 [630;1050]  | 820 [535;1095]  | ns              |
| Hemoglobin (gL)                               | 12.9 [12.0;14.0]* | 12.6 [11.6;13.7]* | 11.3 [10.5;13.0] | 0.0004          |
| h:L (x1000/mmll)                              | 248 [179;331]*  | 247 [189;320]*  | 180 [140;252]   | 0.0007          |
| Serum creatine (mg/L)                         | 288 [234;382]   | 372 [274;531]$^*$ | 361 [277;446]$^*$ | 0.007           |
| Serum creatinine (µg/L)                       | 972 [564;1590]  | 1091 [789;3090] | 1050 [776;2208] | ns              |
| h:L (µg/L)                                    | 37 [33;40]      | 33 [31;37]$^*$  | 33 [29;36]$^*$  | 0.0002          |
| uric acid (mmol/L)                            | 4.06 [3.76;4.40] | 4.09 [3.91;4.30] | 4.14 [3.72;4.48] | ns              |
| Heart rate (mmol/L)                           | 140 [138;143]   | 138 [136;140]   | 140 [137;143]   | 0.04            |
| tricarballytic acid (mmol/L)                  | 2.18 [2.10;2.29] | 2.07 [2.00;2.16]$^*$ | 2.07 [1.97;2.12]$^*$ | 0.000004        |
| nates (mmol/L)                                | 25.9 [23.2;27.5] | 24.5 [22.5;26.7] | 26.1 [23.6;28.9] | ns              |

Ns: not significant

eGFR: estimated glomerular filtration rate

Dunn's post-hoc test p<0.05: * proteinuria stage 3, $ with proteinuria stage 1

Chi² test for categorical variables with Bonferroni correction: * with proteinuria stage 3
Table 3: Multivariable Cox proportional hazards regression analyses in the whole cohorts and in subgroups (categorical variables)
| The whole cohort N=153 | Unadjusted | Model 1 | Model 2 | Model 3 | Model 4 |
|-----------------------|------------|---------|---------|---------|---------|
| **Proteinuria staging (PS)** | PS: Stage 2: 0.35 (0.15-0.84) | age: 1.04 (1.01-1.07) women: 0.25 (0.09-0.68) | age: 1.04 (1.01-1.07) women: 0.27 (0.10-0.74) | age: 1.05 (1.02-1.09) women: 0.33 (0.12-0.92) CRP: 1.01 (1.00-1.01) platelets: 0.99 (0.99-1.00) | age: 1.04 (1.01-1.08) platelets: 0.99 (0.99-1.00) catheter: 3.37 (1.44-7.86) |
| **Tertile of urine α₁-microglobulin (Tα)** | Tα: Tertile 1: 0.19 (0.06-0.55) Tertile 2: 0.23 (0.08-0.61) | Tα: Tertile 1: 0.26 (0.09-0.80) Tertile 2: 0.27 (0.10-0.74) women: 0.30 (0.11-0.83) | Tα: Tertile 1: 0.26 (0.09-0.81) Tertile 2: 0.26 (0.10-0.73) women: 0.32 (0.12-0.86) cancer: 2.57 (1.03-6.42) | Tα: Tertile 1: 0.28 (0.09-0.88) Tertile 2: 0.19 (0.07-0.57) age: 1.04 (1.01-1.08) women: 0.32 (0.12-0.88) CRP: 1.01 (1.00-1.01) | age: 1.04 (1.01-1.08) platelets: 0.99 (0.99-1.00) catheter: 3.37 (1.44-7.86) |
| **Hematuria >10 (Ht)** | Ht: 2.82 (1.32-6.01) | Ht: 2.26 (1.04-4.89) age: 1.04 (1.01-1.07) women: 0.29 (0.11-0.79) | Ht: 2.28 (1.06-4.91) age: 1.04 (1.00-1.07) women: 0.31 (0.11-0.82) cancer: 2.57 (1.03-6.33) | | age: 1.05 (1.01-1.09) women: 0.35 (0.13-0.97) CRP: 1.01 (1.00-1.01) platelets: 0.99 (0.99-1.00) |
| **Urinary catheter (UC)** | UC: 4.18 (1.95-8.95) | UC: 3.72 (1.72-8.02) age: 1.04 (1.01-1.07) women: 0.31 (0.11-0.83) | UC: 3.66 (1.70-7.89) age: 1.04 (1.01-1.08) women: 0.33 (0.12-0.88) | UC: 3.37 (1.44-7.86) | age: 1.04 (1.01-1.09) platelets: 0.99 (0.99-1.00) |

| Cohort with normal eGFR at D0 N=122 | Unadjusted | Model 1 | Model 2 | Model 3 | Model 4 |
|-------------------------------------|------------|---------|---------|---------|---------|
| **Proteinuria staging (PS)** | PS: Stage 2: 0.21 (0.06-0.73) | PS: Stage 2: 0.21 (0.06-0.73) | PS: Stage 2: 0.20 (0.06-0.71) women: 0.20 (0.06-0.71) cancer: 3.86 (1.25-11.96) | PS: Stage 2: 0.27 (0.08-0.98) age: 1.05 (1.01-1.09) cancer: 6.12 (1.82-20.61) CRP: 1.01 (1.01-1.02) | PS: Stage 2: 0.25 (0.07-0.96) age: 1.04 (1.00-1.09) cancer: 6.41 (1.83-22.46) CRP: 1.01 (1.00-1.02) catheter: 4.05 (1.32-12.41) |
| **Tertile of urine α₁-microglobulin** | Tα: Tertile 3: 4.60 | Tα: Tertile 3: 4.50 | Tα: Tertile 3: 4.49 | Tα: Tertile 3: 4.18 (1.50-11.72) | Tα: Tertile 3: 4.12 (1.45-11.67) |
| (Tα) | (1.78-11.90) | (1.74-11.65) | (1.73-11.61) | cancer: 3.60 (1.16-11.11) | cancer: 4.90 (1.50-16.01) | CRP: 1.01 (1.01-1.02) | cancer: 4.80 (1.48-15.63) | CRP: 1.01 (1.01-1.02) | Hematuria: 3.00 (1.11-8.15) |
|---|---|---|---|---|---|---|---|---|---|
| Hematuria >10 | Ht: 5.14 (1.99-13.27) | Ht: 4.36 (1.66-11.44) | Ht: 5.28 (2.04-13.69) | cancer: 4.11 (1.33-12.72) | Ht: 3.17 (1.15-8.72) | age: 1.05 (1.01-1.09) | cancer: 3.99 (1.26-12.62) | CRP: 1.01 (1.00-1.01) |
| Urinary catheter (UC) | UC: 6.68 (2.58-17.27) | UC: 6.94 (2.68-17.99) | UC: 6.84 (2.64-17.73) | cancer: 4.07 (1.32-12.63) | UC: 3.88 (1.31-11.51) | age: 1.05 (1.01-1.09) | cancer: 3.74 (1.19-11.77) | CRP: 1.01 (1.00-1.01) |
| **Cohort without urinary catheter** N=114 | | | | | | | | | |
| Proteinuria staging (PS) | PS: Stage 3: 9.28 (2.03-42.39) | PS: Stage 3: 9.28 (2.03-42.39) | PS: Stage 3: 6.69 (1.46-30.73) | CRP: 1.01 (1.00-1.02) | platelets: 0.99 (0.98-1.00) | PS: Stage 3: 6.69 (1.46-30.73) | CRP: 1.01 (1.00-1.02) | platelets: 0.99 (0.98-1.00) |
| Tertile of urine α1-microglobulin (Tα) | Tα: Tertile 3: 5.97 (1.80-19.85) | Tα: Tertile 3: 5.97 (1.80-19.85) | Tα: Tertile 2: 0.09 (0.01-0.56) | eGFR: 0.97 (0.95-0.98) | CRP: 1.02 (1.01-1.04) | Tα: Tertile 2: 0.07 (0.01-0.56) | age: 1.08 (1.01-1.14) | CRP: 1.03 (1.01-1.04) | Hematuria: 5.12 (1.34-21.11) |
| Hematuria >10 | ns | age: 1.05 (1.01-1.10) | age: 1.05 (1.01-1.10) | CRP: 1.02 (1.01-1.03) |

Ns: not significant

eGFR: estimated glomerular filtration rate

Model 1: adjusted for age and gender

Model 2: Model 1+ adjusted for CKD history and active cancer

Model 3: Model 2+ adjusted for eGFR, CRP and platelet counts

Model 4: Model 3+ adjusted for hematuria and urinary catheter

**Figures**
Figure 1

A: Survival curve according to proteinuria staging B: Survival curve according to urine α₁-microglobulin C: Survival curve according to presence of hematuria

Supplementary Files
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