Nephrosclerosis impacts time trajectory of renal function and outcomes in elderly individuals with chronic kidney disease

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Accepted 25 May 2021
Published Online First 14 June 2021

To cite: Zicarelli MT, Patella G, Bolignano D, *et al*. *J Investig Med* 2021;**69**:1411–1416.

ABSTRACT

Despite hypertension ranks among the leading causes of chronic kidney disease (CKD), the impact of chronic hypertensive nephropathy, the so-called 'nephrosclerosis' (NS), on CKD progression is often unpredictable, particularly in elderly population. We have conducted a prospective, observational study to define renal function patterns and outcomes in elderly CKD individuals with or without NS. Three hundred four individuals with an already established CKD were categorized according to the etiology of CKD. NS was defined as the presence of CKD associated with long-term essential hypertension, hypertensive retinopathy, left ventricular hypertrophy and minimal proteinuria. Time trajectories in estimated glomerular filtration rate (eGFR) (CKD-Epi) were computed over a 4-year follow-up. In addition, we analyzed the occurrence of a composite outcome of doubling of serum creatinine levels, eGFR reduction ≥25% and/or the need of chronic renal replacement therapy. CKD was secondary to nephrosclerosis (CKD-NS) in 220 (72.3%). In the whole cohort, the average estimated annual GFR slope was 1.8 mL/min/1.73 m^2. eGFR decline was slower in CKD-NS as compared with others (1.4 vs 3.4 mL/min/1.73 m^2; p<0.001). The composite renal outcome during follow-up occurred less frequently among elderly with CKD-NS (16/204 vs 14/70; p=0.01, crude HR 0.43, 95% CI 0.22 to 0.85) and was associated at logistic analyses with the etiology of CKD, background cardiovascular disease, total and low density lipoproteins (LDL) cholesterol, and glycemia levels (p value was ranging from 0.01 to 0.05). Despite being highly prevalent in the elderly, NS is associated with a more favorable renal disease course as compared with other conditions.

Significance of this study

What is already known about this subject?

- 'Nephrosclerosis' (NS) is a nosological entity wrongly defined in the past as the 'Cinderella' of renal diseases but conversely today it is prevalent in elderly with total loss of renal function in replacement therapy.
- Elderly with chronic kidney disease (CKD) receive often an etiologic diagnosis of NS.
- NS is characterized by the presence of renal function loss associated with long-term benign hypertension, hypertensive retinopathy, left ventricular hypertrophy and minimal proteinuria.

What are the new findings?

- The present paper adds new information regarding different epidemiology of CKD in elderly patients pointing out the need of take care to 'nephrosclerosis'.
- In this paper, elderly patients with CKD associated with NS seem to experience a better renal disease course overtime, in terms of either a more stable eGFR slope or a less frequent occurrence of sudden renal function worsening.

How might these results change the focus of research or clinical practice?

- The etiology of CKD should be better characterized also in elderly.
- In elderly, therapeutic efforts should go beyond just optimizing blood pressure control and focus mainly on concomitant diseases.
- A better management of NS has an economic and social impact on health system.

INTRODUCTION

During the last decades, global mortality has dramatically decreased in Western countries, mainly as the consequence of a progressive decline in cardiovascular and cerebrovascular morbidity with less cigarette smoking, a better management of hypertension, the extensive use of statins and the timely use of thrombolysis and arterial stenting to limit or prevent cardiovascular accidents.[1–4] These advances in public health, leading to an overall increase in the lifespan, have also profoundly modified the

spectrum of kidney diseases in the elderly and, particularly, the epidemiological characteristics of the population receiving a generic diagnosis of chronic kidney disease (CKD).

With advancing age, CKD has nowadays become more related to the long-time exposure to essential hypertension, to the progression of chronic atherosclerosis with renal vessel adaptations and to a physiological but substantial loss of nephrons.[5] In the third National Health and Nutrition Examination Survey (NHANES III), 35% of the elderly population had stage 3 CKD,[6] and in the US population, the prevalence of renal impairment in persons older than 70 years resulted as high as 15%.[7] In a rising number of elderly individuals, incident CKD is frequently being attributed to a pathological entity defined as '*nephrosclerosis*', which is characterized by the presence of renal function loss associated with long-term benign hypertension, hypertensive retinopathy, left ventricular hypertrophy and minimal proteinuria.[8 9] Hypertension remains largely prevalent among patients with CKD, particularly in older individuals,[10] but age also impacts on the frequency distribution of the primary diseases leading to a frank renal function impairment.[11] Yet, few studies to date have specifically investigated the rate of CKD progression in elderly populations in relation to the type of primary renal disease. In particular, it remains a timely object of debate whether nephrosclerosis (NS), despite being a very prevalent condition, may trigger better or worse renal outcomes in this particular population setting, as compared with other causes of CKD. Keeping this background in mind, we have therefore conducted an observational, prospective cohort study to compare the evolution of renal function overtime in elderly CKD individuals with or without NS and to identify possible clinical predictors of different renal outcomes.

METHODS

Patients selection and baseline assessment

Three-hundred and four consecutive elderly patients (age ≥65) hospitalized with an admitting diagnosis of CKD at the Nephrology Unit of the *Magna Graecia* University Hospital of Catanzaro (Italy) were enrolled in the study, which was approved by the local Ethic Committee. All patients gave written informed consent to participate. Inclusion criteria were the presence of non-advanced CKD (NFK stages 1–4) and a stable renal function with no documented transitory or permanent doubling in serum creatinine levels over the last 6 months before starting the study. Patients' history was carefully documented by interview, also recording drug prescription and etiology of their CKD with histological diagnosis, when available. NS was defined as the presence of CKD associated with long-term essential hypertension (>10 aa), hypertensive retinopathy, left ventricular hypertrophy as documented by echocardiography and minimal proteinuria (<1 g/24 hours). Clinical examination was performed, including assessment of blood pressure, body mass index (BMI) and blood glucose. Common biochemical parameters were measured at baseline in all patients, according to standard methods in the routine clinical laboratory. Glomerular filtration rate was estimated (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Prospective follow-up

After the baseline assessment, patients were prospectively followed up until the end of an established 4-year observational period. During this period, clinical data were checked and recorded at least on an annual basis. Renal function trajectories were computed either in a quantitative manner by analyzing time trends of eGFR over a minimum of five timepoints and also by analyzing the occurrence of a composite endpoint of doubling of serum creatinine, eGFR decrease ≥25% from baseline values and/or end-stage kidney disease requiring chronic renal replacement therapy by dialysis or renal transplantation. Patients were personally contacted in case they missed any appointment and at the study end date in order to avoid eventual loss to follow-up. Patients who died before completing the follow-up were excluded from the study in order to avoid competing risk in the renal endpoint analysis.

Statistical analyses

Statistical analyses were performed using the SPSS package (V.24.0; IBM Corporation) and the MedCalc Statistical Software (V.14.8.1; MedCalc Software bvba).

Data were presented as mean±SD for normally distributed values (at Kolmogorov-Smirnov test), median (IQ range) for variables with skewed distribution or frequency percentage. Differences between groups were determined by the unpaired t-test for normally distributed values, the Mann-Whitney U test for non-parametric values and the χ^2 test followed by a Fisher's exact test for frequency distributions. One-way analysis of variance (ANOVA) with linear assumption was employed to analyze statistical variance of eGFR overtime (p for trend). Pairwise comparison by the Bonferroni's test was used to check differences in eGFR time trends between subpopulations. Bivariate logistic regression analyses were performed to establish significant predictors of the composite renal outcome. All results were considered significant if the p value was ≤0.05.

RESULTS

Baseline characteristics

The final study cohort consisted of 304 elderly patients with CKD. Mean age was 69±4 years and the majority of them were male (n:194; 64.1%). Prevalence of diabetes was 53.6%. Baseline mean eGFR was 44.2±19.6 mL/min/1.73 m^2 with a mean serum creatinine of 1.99±0.90 mg/dL. Median proteinuria was 0.4 (IQR 0.1–0.9) g/24 hours. Hypertension was highly prevalent (83.8%) in the whole cohort, with angiotensin converting enzyme-inhibitor (ACEi) (83.8%) and angiotensin receptor blockers (ARBs) (57.9%) being the most used antihypertensive drugs. The etiology of CKD was presumed due to NS in 220 (72.3%) patients. Among the remaining 84 (27.7%), glomerular diseases were the most frequent cause of CKD (n=39; 47.6%), followed by diabetic nephropathy (n=22; 26.1%), miscellaneous causes (n=16;17.8%), interstitial/pyelonephritis (n=4; 4.7%) and cystic diseases (n=3; 3.5%). Table 1 depicts the main clinical characteristics and biopsy findings of the study population. Table 2 summarizes histological data from 61 patients with biopsy-proven glomerulonephritides.

Table 1 Baseline demographic, somatometric and clinical data of the study population

	Whole cohort (N=304)	Nephrosclerosis (N=220; 72.3%)	Other kidney diseases (N=84; 27.7%)	p value
Age (years)	69±4	70±4	68±3	0.16
Male sex, n (%)	194 (64.1)	139 (63.2)	55 (65.5)	0.70
BMI (kg/m^2)	27.5±4.1	28.1±5.2	27.1±4.3	0.07
Systolic blood pressure (mm Hg)	133±18	139±14	132±27	0.06
Diastolic blood pressure (mm Hg)	75±11	76±11	73±12	0.23
Diabetes, n (%)	163 (53.6)	138 (62.7)	25 (29.7)	<0.001
Total cholesterol (mg/dL)	172±46	159±52	181±49	0.004
HDL cholesterol (mg/dL)	51±24	50±11	51±28	0.21
LDL cholesterol (mg/dL)	109±42	103.3±40.9	119.5±41.1	0.03
Hemoglobin (g/dL)	13.2±1.9	13.1±1.8	13.2±1.4	0.56
eGFR (mL/min/1.73 m^2)	44.2±19.6	41.0±17.1	70.8±28.2	<0.001
Creatinine (mg/dL)	1.99±0.90	2.08±0.68	1.62±0.83	0.01
Glycemia (mg/dL)	117±17	126±19	109±23	0.04
Proteinuria (g/24 hours)	0.4 [0.1–0.9)	0.2 [0.1–0.8)	0.6 [0.2–1.5)	<0.001
Urinary sodium (mg/24 hours)	133±35	136±31	130±19	0.08
Vitamin D (mcg/dL)	24.3±15.7	24.7±11.1	24.1±12.0	0.31
Statins use, n (%)	127 (41.7)	105 (48.6)	27 (32.1)	0.01
ESAs use, n (%)	37 (12.1)	28 (12.7)	9 (10.7)	0.63
Anti-hypertensive drugs, n (%)				
Diuretics	92 (30.2)	70 (31.8)	22 (26.1)	0.66
Beta blockers	45 (14.8)	35 (15.9)	10 (11.9)	0.37
ARBs	176 (57.9)	111 (50.4)	65 (76.4)	<0.001
ACEi	255 (83.8)	175 (79.5)	80 (95.2)	0.006
CCBs	77 (25.3)	69 (31.3)	8 (9.5)	<0.001
History of CV disease, n (%)				
TIA/Stroke	30 (10)	29 (13.1)	1 (1.2)	<0.001
Peripheral vascular disease	45 (14.8)	43 (19.5)	2 (2.3)	<0.001
Ischemic heart disease	31 (10.2)	28 (12.7)	3 (3.5)	0.02

ACEi, angiotensin converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESAs, erythropoietin-stimulating agents; HDL, high density lipoproteins; LDL, low density lipoproteins; TIA, transient ischemic attack.

Baseline differences between elderly CKD patients with or without NS

Elderly patients with NS did not differ from others with respect to mean age, gender, BMI, blood pressure levels, hemoglobin, vitamin D and urinary sodium (p value ranging from 0.06 to 0.63). Conversely, in these individuals, there was a higher prevalence of diabetes (p<0.001), which translated into higher baseline glycemic levels (p=0.04), and significantly lower LDL and total cholesterol levels (p=0.03 and 0.004, respectively), which were associated with a higher prevalence of statins users (p=0.01). Patients with NS also exhibited an increased frequency of background CV diseases and were more likely on calcium channel blockers (p<0.001), while those with CKD secondary to other conditions were more frequently prescribed with ACEi (p=0.006) or ARBs (p<0.001). With respect to kidney impairment, patients with NS exhibited a significantly worsen renal function (eGFR: 41±17.1 vs 70.8±28.2 mL/min/1.73 m^2, p<0.001; serum creatinine: 2.08±0.68 vs 1.62±0.83, p=0.01), but lower proteinuria levels (0.2 (0.1–0.8) vs 0.6 (0.2–1.5) g/24 hours; p<0.001). Differences between the two subpopulations are highlighted in table 1.

Table 2 Histological data from 61 patients with biopsy-proven glomerulonephritides

Type of glomerulonephritis	n	%
Membranous	29	47.5
Membranoproliferative	3	4.9
IgA nephropathy	2	3.3
Focal/Segmental	5	8.2
Diabetic nephropathy	22	36.1

Follow-Up and renal outcomes

After the baseline assessment, patients were prospectively followed up in order to assess longitudinal changes in renal function and the occurrence of the composite renal outcome.

Figure 1 depicts the time trend of renal function during follow-up. The average estimated annual GFR decline in the whole cohort during follow-up was 1.8 mL/min/1.73 m^2 (mean difference in eGFR end of follow-up to baseline=−8.80 mL/min/1.73 m^2; 95% CI −12.02 to −5.58; p for trend <0.001). Individuals with NS experienced a slower eGFR decrease as compared with others (estimated annual loss: 1.4 vs 3.4 mL/min/1.73 m^2; pairwise comparison

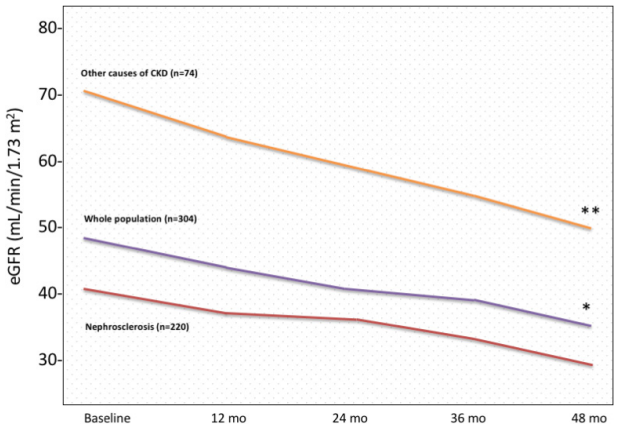

Figure 1 Time trend of average eGFR over the 4-year follow-up in the whole study population and in subcategories of elderly individuals with or without nephrosclerosis. *p for trend <0.001. **Pairwise comparison difference with nephrosclerosis p<0.001. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

difference between means: −23.19 mL/min/1.73 m^2; 95% CI −31.01 to −15.38; p<0.001). No differences were observed in eGFR loss in patients stratified according to the presence or absence of diabetes (p=0.26).

During follow-up, 30 out of 304 patients (9.86%) experienced the composite outcome of doubling of serum creatinine, eGFR decrease ≥25% from baseline and/or end stage renal disease (ESKD) requiring chronic renal replacement therapy. The endpoint occurred less frequently among elderly individuals with NS as compared with others (16/220 (7.3%) vs 14/84 (16.7%); p=0.01) with a crude risk ratio of 0.43 (95% CI 0.22 to 0.85). At baseline, CKD progressors showed higher BMI (p=0.04), total cholesterol (p=0.01), LDL cholesterol (p=0.03) and glycemia (p=0.04) as compared with non-progressors; furthermore, they were more frequently on erythropoietin-stimulating agent therapy (p=0.05) and had a more frequent history of CV disease (p=0.04) (table 3). Logistic regression analyses confirmed associations between the renal outcome and NS as the cause of CKD (OR 0.426; 95% CI 0.225 to 0.747; p=0.01), history of (any) CV disease (OR 1.125; 95% CI 1.003 to 1.243; p=0.04), total cholesterol (OR 1.158; 95% CI 1.011 to 1.353; p=0.03), LDL cholesterol (OR 1.160; 95% CI 1.024 to 1.378;p=0.02) and glycemia (OR 1.099; 95% CI 1.002 to 1.157; p=0.05) (table 4).

DISCUSSION

In this prospective cohort study, we have found that elderly patients with CKD due to NS experienced a significantly slower renal function decline over a 4-year follow-up as compared with those with CKD due by other etiologies, including diabetic nephropathy and glomerular diseases. Similarly, these subjects presented a lower crude risk of CKD progression (relative risk 0.43; 95% CI 0.22 to 0.85), as defined by the occurrence of a composite renal endpoint encompassing an absolute doubling of serum creatinine, eGFR decrease and/or the need for chronic renal replacement therapy. Of note, such an apparent clinical advantage was confirmed at logistic regression analyses, in which

Table 3 Differences in main characteristics of elderly patients with CKD experiencing the composite renal outcome (CKD progressors) as compared with others (non-progressors)

	CKD progressors (N=30; 9.86%)	Non-progressors (N=274; 90.1%)	p value
Age (years)	71±8	68±5	0.22
Male sex, n (%)	17 (56.6)	177 (64.5)	0.39
BMI (kg/m^2)	29.2±4.0	25.3±6.1	0.04
Systolic blood pressure (mm Hg)	144±21	139±26	0.16
Diastolic blood pressure (mm Hg)	81±16	75±12	0.12
Diabetes, n (%)	20 (66.6)	143 (52.1)	0.10
Total cholesterol (mg/dL)	171±44	135±39	0.01
HDL cholesterol (mg/dL)	52±13	51±22	0.55
LDL cholesterol (mg/dL)	133.4±46.7	106.4±38.8	0.03
Hemoglobin (g/dL)	12.8±2.7	13.0±2.1	0.61
eGFR (mL/min/1.73 m^2)	49.5±22.1	66.3±19.2	0.13
Creatinine (mg/dL)	1.76±0.71	1.49±0.88	0.19
Glycemia (mg/dL)	138±15	110±13	0.04
Proteinuria (g/24 hours)	0.4 (0.1–0.9)	0.4 (0.01–0.6)	0.32
Urinary sodium (mg/24 hours)	133±37	129±39	0.27
Vitamin D (mcg/dL)	24.9±14.0	23.7±11.8	0.46
Statins use, n (%)	16 (53)	111 (40.5)	0.17
ESAs use, n (%)	7 (23.3)	30 (10.9)	0.05
Antihypertensive drugs			
Diuretics, n (%)	12 (40)	80 (29.9)	0.22
Beta-blockers, n (%)	7 (23.3)	38 (13.8)	0.16
ARBs, n (%)	20 (66.6)	156 (56.9)	0.30
ACEi, n (%)	23 (76.6)	232 (84.6)	0.25
CCBs, n (%)	8 (26.6)	69 (25.1)	0.85
History of CV disease, n (%)	29 (97)	226 (82)	0.04
Etiology of CKD, n (%)			
Nephrosclerosis	16 (53)	204 (74.4)	0.01
Other	14 (47)	70 (25.6)	

ACEi, angiotensin converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESAs, erythropoietin-stimulating agents; HDL, high density lipoproteins; LDL, low density lipoproteins.

NS ranked as the strongest variable (inversely) associated with the outcome of interest. NS has been described as the consequence of protracted time exposure to benign essential hypertension leading in advanced age to a gradual loss of renal function. In fact, the kidneys are highly vascularized and extremely sensitive to any decrease in blood flow; therefore, both arterial hypertension and the loss of microvascularization induced by atherosclerosis may cause renal

Table 4 Clinical variables significantly associated with the combined renal outcome at logistic regression analyses

	OR	95% CI	p value
Glycemia	1.099	1.002 to 1.157	0.05
History of any CV disease	1.125	1.003 to 1.243	0.04
Total cholesterol	1.158	1.011 to 1.353	0.03
LDL cholesterol	1.160	1.024 to 1.378	0.02
Nephrosclerosis as cause of CKD	0.426	0.225 to 0.747	0.01

CKD, chronic kidney disease; CV, cardiovascular; LDL, low density lipoproteins; NS, nephrosclerosis.

hemodynamic deterioration with chronic lesions of the ischemic tissue and hypoxia.[12 13] In individuals with long-term benign hypertension, constant moderate high levels of systolic and diastolic blood pressure trigger a specific adaptation of renal vascular, glomerular and tubule-interstitial structures. Renal vessels develop medial hypertrophy and fibroblastic intimal thickening with a reduction of vascular lumen,[14] while glomeruli may present with focal global and/or segmental sclerosis with following interstitial fibrosis.[15] As age advances, subjects become also exposed to chronic atherosclerosis which may contribute to further aggravate the above-mentioned renal lesions.[16 17]

Despite this, NS has always been described as a slowly progressive condition, with the majority of elderly patients never progressing to end-stage kidney disease requiring chronic renal replacement therapy.[18–20]

In our study, the overall average decline in eGFR over a 4-year observation period was of 1.8 mL/min/year. This finding is in agreement with observations reported by larger studies at the community level, estimating an annual average renal function loss after the fifth decade of life ranging from 0.5 to 2.6 mL/min/year.[21 22]

Of note, in our study, elderly individuals with NS displayed an estimated annual loss of 1.4 mL/min/year, which was remarkably lower to that observed in the miscellaneous group of those with CKD associated with other diseases (3.4 mL/min/year).

These findings echo those reported in a larger, community-based cohort of elderly subjects in which the progression of CKD was assessed by serial serum creatinine measurement over a shorter follow-up period.[23] Interestingly, despite diabetes remains a key risk factor for renal disease progression, no differences in eGFR slope were observed in patients stratified according to the presence or absence of this condition. Similarly, CKD progression was apparently not influenced by gender but elderly individuals manifesting a rapidly progressing disease showed a worsen cardiac risk profile, including higher BMI and cholesterol levels and a more evident history of CV diseases.

Aging conveys per se an increased risk of experiencing more than one chronic condition at the same time. It is simplistic to consider the burden from each of these conditions independently. Renal function decline could be slowed down if other comorbidities are effectively managed and particularly if these are detected early enough to avoid renal failure.[24–26] The European Renal Best Practice Group Guideline recently included overall strategies for older and frail patients and advised regularly screening for functional impairment and malnutrition to recognize patients that could take advantage for more intensive care.[27] In our study, it is interesting to point out that elderly patients with CKD due to NS manifested a significantly worsen renal function at baseline, as compared with others (eGFR: 41±17.1 vs 70.8±28.2 mL/min/1.73 m^2, $p<0.001$). This apparently unexpected report assumes foremost importance, bearing in mind that baseline eGFR usually ranks among the most relevant confounders in longitudinal studies looking at CKD progression. Therefore, in elderly individuals with CKD, NS may confer a more favorable course of kidney failure over other renal diseases, even in the presence of a more severely impaired renal function.

We believe that our study has some strengths and limitations that deserve mentioning. We have assembled a relatively wide and homogeneous cohort of elderly persons with non-advanced CKD which have systematically been followed for a relatively long time period. This allowed us to depict reliable renal function trajectories according to various renal diagnoses in the most accurate way possible and taking into account different covariates. Nevertheless, the observed rate of the established composite renal outcome was unexpectedly low (~10%); despite the number of individuals reaching this endpoint was statistically lower among those with NS, such a limited rate prevented us to perform more complex survival analyses and proportional hazard regression to adjust the crude risk for multiple confounders. Finally, and no less important, given the observational nature of the study, the presence of selection bias, confounding by indication and residual confounding by unmeasured or unknown variables cannot be fully ruled out, therefore hampering the overall applicability of our findings to other cohorts. Furthermore, the lack of some parameters such as serum bicarbonate as acidosis is a known risk factor for progression of CKD.

In conclusion, we have demonstrated that elderly patients with CKD associated with NS seem to experience a better renal disease course overtime, in terms of either a more stable eGFR slope or a less frequent occurrence of sudden renal function worsening. Future studies on larger and heterogeneous cohort are advocated to confirm these findings. Therapeutic efforts to delay CKD progression in older populations should go beyond the mere optimization of blood pressure control and focus more on concomitant diseases.

Contributors All authors contributed to the conceptualization, design, data collection, interpretation, and preparation of this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval (1) Ethic Committee Comitato Etico Area Centro, Regione Calabria. (2) Approval ID No. 28 of 2020.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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