VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2023, Vol. 30, No. 5, 781–789
DOI: 10.5603/CJ.a2022.0105

ISSN 1897–5593
eISSN 1898–018X

Renal dysfunction and outcome in left ventricular non-compaction

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Abstract

Background: *While renal function has been observed to inversely correlate with clinical outcome in other cardiomyopathies, its prognostic significance in patients with left ventricular non-compaction cardiomyopathy (LVNC) has not been investigated. The aim of this study was to determine the prognostic value of renal function in LVNC patients.*

Methods: *Patients with isolated LVNC as diagnosed by echocardiography and/or magnetic resonance imaging in 4 Swiss centers were retrospectively analyzed for this study. Values for creatinine, urea, and estimated glomerular filtration rate (eGFR) as assessed by the CKD-EPI 2009 formula were collected and analyzed by a Cox regression model for the occurrence of a composite endpoint (death or heart transplantation).*

Results: *During the median observation period of 7.4 years 23 patients reached the endpoint. The age- and gender-corrected hazard ratios (HR) for death or heart transplantation were: 1.9 (95% confidence interval [CI] 1.4–2.6) for each increase over baseline creatinine level of 30 μmol/L ($p < 0.001$), 1.6 (95% CI 1.2–2.2) for each increase over baseline urea level of 5 mmol/L ($p = 0.004$), and 3.6 (95% CI 1.9–6.9) for each decrease below baseline eGFR level of 30 mL/min ($p \leq 0.001$). The HR (log2) for every doubling of creatinine was 7.7 (95% CI 3–19.8; $p < 0.001$), for every doubling of urea 2.5 (95% CI 1.5–4.3; $p < 0.001$), and for every bisection of eGFR 5.3 (95% CI 2.4–11.6; $p < 0.001$).*

Conclusions: *This study provides evidence that in patients with LVNC impairment in renal function is associated with an increased risk of death and heart transplantation suggesting that kidney function assessment should be standard in risk assessment of LVNC patients.* (Cardiol J 2023; 30, 5: 781–789)

Key words: renal function, kidney, urea, estimated glomerular filtration rate, creatinine, prognosis, heart failure

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Received: 11.08.2022 Accepted: 10.10.2022 Early publication date: 7.11.2022

Introduction

Left ventricular non-compaction cardiomyopathy (LVNC) is a potentially life-threatening disease, characterized by a thin, compacted outer layer and a thick, non-compacted inner layer with deep recesses between prominent trabeculations [1, 2]. Symptomatic patients typically present with heart failure, ventricular arrhythmias or thromboembolic events [3–5]. However, the clinical course of patients is variable and the need for identifying factors which relate to adverse outcomes and subsequent mortality remains crucial. Previous studies showed, that left ventricular ejection fraction (LVEF), right ventricular size and systolic function, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), exercise capacity and heart failure symptoms can predict outcome [6–8].

In patients with chronic heart failure impaired renal function seems to be consistently associated with a worse prognosis independent of other risk factors [9–15]. In non-ischemic cardiomyopathy, moderate renal insufficiency was an independent risk factor for cardiac events, even in patients with only mild to moderate symptoms [16–18]. A similar relationship was observed in takotsubo cardiomyopathy, where lower estimated glomerular filtration rate (eGFR) values during hospitalization were associated with longer hospitalizations and higher rates of adverse events [19].

According to available research, no studies have evaluated renal function and its prognostic value among patients with LVNC. The aim of this study was to evaluate renal function and its prognostic role in patients with LVNC.

Methods

Patients and data collection

All patients diagnosed with LVNC between 1988 and 2016, fulfilling the echocardiographic criteria described by Jenni et al. [20] were identified from databases at the University Hospitals Zurich, Basel, Geneva, and St. Gallen. Patients with at least 1 measurement of creatinine were included in this retrospective analysis. The study was approved by the local ethical committees and informed consent was obtained from all participants.

Demographic and clinical data as well as echocardiography data were collected retrospectively and entered into a web-based database (SecuTrial, Berlin, Germany) hosted by the Clinical Trial Center at the University of Zurich. Entry into study was defined as the first visit in one of the study hospitals when at least one parameter was recorded. All values for creatinine and urea at baseline and follow-ups were collected and eGFR was assessed by the CKD-EPI formula [21]. Serum creatinine level was measured in each center based on certified protocols [22–24].

The endpoint was defined as the occurrence of death by any cause or need for heart transplantation as assessed in hospital records as well as by telephone survey.

Statistical analysis

Statistical analysis of the time-to-event data was performed using the Cox proportional hazard models with age as time scale (with or without adjustment for age and gender), so patients were treated as left-truncated at their age of entry. In order to check for non-informative late entry, the age at entry of a patient was included in the adjusted models, without showing a significant effect [25]. Time-dependent variation of the covariates creatinine, urea, and eGFR was taken into account by creating a data set listing the time-dependent covariates for each follow-up visit of a patient and the time span during which the values of the covariates did not change [26]. In case of a violation of the proportional hazards assumption, it was examined by plotting the scaled Schoenfeld residuals against time (age of patient) and by applying the test developed by Grambsch and Therneau [27], the covariate was modeled using a time-dependent coefficient (linear time scale), and hazard ratios were assessed for different ages separately. In the analysis of different cut-offs, a minimum of two events were considered per group, and was necessary to avoid complete separation. Statistical software for the R programming language were used.

Results

Patients and sample size

During 1025 person-years (longest follow-up 18.7 years) 23 (18%) patients died or underwent heart transplantation. An overview of the study population and its baseline characteristics is provided in Table 1. Table 2 provides data of patients reaching the endpoint. All 126 patients had in total 888 creatinine measurements resulting in 888 eGFR calculations. A subset of 94 patients had in total 667 urea measurements. All data points were included in the analysis.

Table 1. Overview of baseline patient characteristics.

	All patients	Patients not reaching the endpoint	Patients reaching endpoint
Number of patients	126	103	23
Age [years]	45.7 ± 16.9	44.6 ± 17.1	50.8 ± 15.6
Female	41 (32.5%)	36 (34.9%)	5 (21.7%)
Systolic blood pressure [mmHg]	122 ± 20.90	124±19.05	111 ± 26.08
Diastolic blood pressure [mmHg]	75 ± 12.01	75 ± 10.80	70 ± 17.74
Heart rate [bpm]	75 ± 18.72	74 ± 17.60	79 ± 22.50
Left ventricular ejection fraction [%]	41 ± 17.30	43 ± 16.67	28 ± 14.40
Medication:			
Beta-blockers	50 (39.7%)	38 (36.9%)	11 (47.8%)
ACE-inhibitor	47 (37.3%)	29 (28.1%)	17 (74.0%)
AT-2 antagonist	14 (11.1%)	10 (9.7%)	4 (17.4%)
Aldosterone antagonist	19 (15.1%)	11(10.7%)	8 (34.8%)
Calcium antagonist	5 (3.9%)	4 (3.9%)	0 (0.0%)
Diuretics	53 (42.1%)	34 (33.0%)	18 (78.2%)
Digitalis	10 (7.9%)	5 (4.8%)	5 (21.7%)
ASA	22 (17.4%)	17 (16.5%)	5 (21.7%)
Statin	11 (8.7%)	6 (5.8%)	4 (17.4%)
Anticoagulant	38 (30.2%)	24 (23.3%)	13 (56.5%)

Values are given as mean ± standard deviation or numbers (percentages); ACE — angiotensin-converting enzyme; ASA — acetylsalicylic acid; AT-2 — angiontensin 2

Table 2. Course of patients reaching the endpoint.

	Baseline measurement	Last measurement before reaching the endpoint
Systolic blood pressure [mmHg]	111 ± 26.08	94 ± 24.35
Diastolic blood pressure [mmHg]	70 ± 17.74	61 ± 16.83
Heart rate [bpm]	79 ± 22.50	77.60 ± 18.57
Left ventricular ejection fraction [%]	28 ± 14.40	28 ± 14.01
Medications:		
Beta-blockers	11 (47.8%)	13 (56.5%)
ACE-inhibitor	17 (74.0%)	9 (39.1%)
AT-2 antagonist	4 (17.4%)	6 (26.1%)
Aldosterone antagonist	8 (34.8%)	7 (30.4%)
Calcium antagonist	0 (0.0%)	1 (4.3%)
Diuretics	18 (78.2%)	13 (56.5%)
Digitalis	5 (21.7%)	1 (33.3%)
ASA	5 (21.7%)	1 (4.3%)
Statin	4 (17.4%)	5 (21.7%)
Anticoagulant	13 (56.5%)	14 (60.8%)

Values are given as mean ± standard deviation or numbers (percentages); ACE — angiotensin-converting enzyme; ASA — acetylsalicylic acid; AT-2 — angiontensin 2

Table 3. Baseline and last measurement of creatine, urea and estimated glomerular filtration rate (eGFR) for all patients, patients reaching the endpoint and patients not reaching the endpoint.

	Baseline measurement	Last measurement
All patients (n = 126)		
Creatinine [μmol/L]	87 (74–106)	85 (75.5–102)
Urea [mmol/L]	6.1 (4.4–8.1)	5.9 (4.5–7.4)
eGFR [mL/min]	85.5 (68.2–95.8)	82.5 (64.5–97.8)
Patients not reaching the endpoint (n = 103)		
Creatinine [μmol/L]	84 (73–102)	83 (73–95.5)
Urea [mmol/L]	5.5 (4.2–7.0)	5.8 (4.25–7)
eGFR [mL/min]	89 (70.5–96.5)	89 (68–101)
Patients reaching the endpoint (n = 23)		
Creatinine [μmol/L]	94 (84.5–106)	112 (82.5–146)
Urea [mmol/L]	7.9 (5.8–9.4)	6.8 (5.1–9.7)
eGFR [mL/min]	73 (63.5–89.5)	68 (50–76)

Values are given as mean ± standard deviation or numbers (percentages).

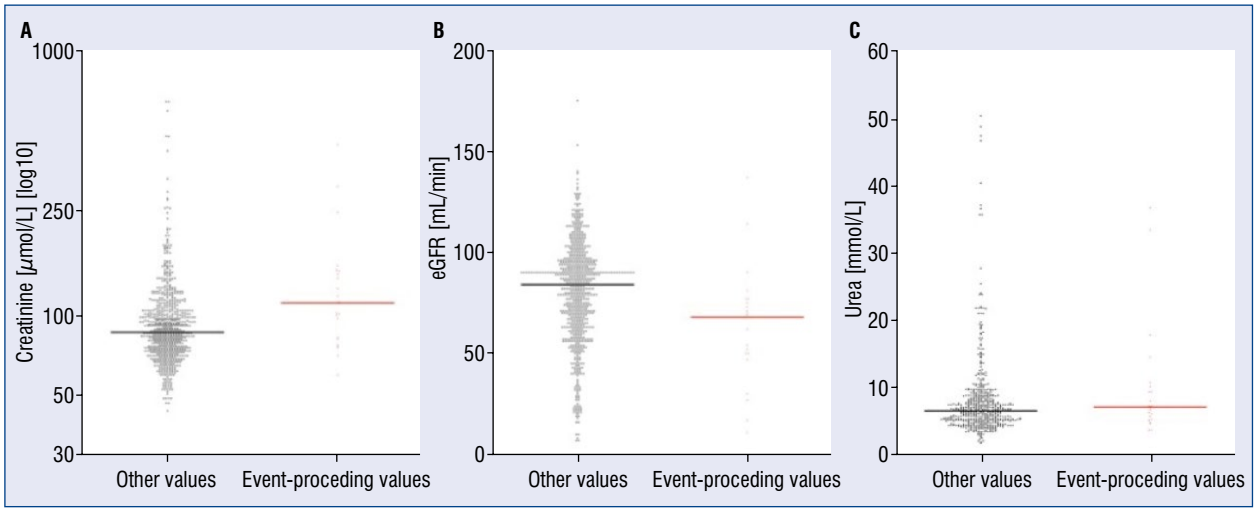

Figure 1. A. Creatinine over time and before an event (death or heart transplantation). Dot plot charts representing values of creatinine measurements over time except event-preceding measurements in all patients, and event-preceding measurements in patients reaching the endpoint. The horizontal line indicates the median value. The y-axis is depicted in a log10-scale; **B.** Estimated glomerular filtration rate (eGFR) over time and before an event (death or heart transplantation). Dot plot charts representing values of eGFR over time except event-preceding measurements in all patients, and event-preceding measurements in patients reaching the endpoint. The horizontal line indicates the median value; **C.** Urea over time and before an event (death or heart transplantation). Dot plot charts representing values of urea measurements over time except event-preceding measurements in all patients, and event-preceding measurements in patients reaching the endpoint. The horizontal line indicates the median value.

Baseline and event-preceding kidney function

The median creatinine, urea, and eGFR levels at baseline of all patients, as well as separately for patients not reaching the endpoint and patients reaching the endpoint are depicted in Table 3. Median last measurements of patients reaching the endpoint was for creatinine 112 (interquartile range [IQR] 82.5–146) μmol/L, for urea 6.8 (5.1–9.7) mmol/L, and for eGFR 68 (50–76) mL/min (Table 3, Figs. 1, 2).

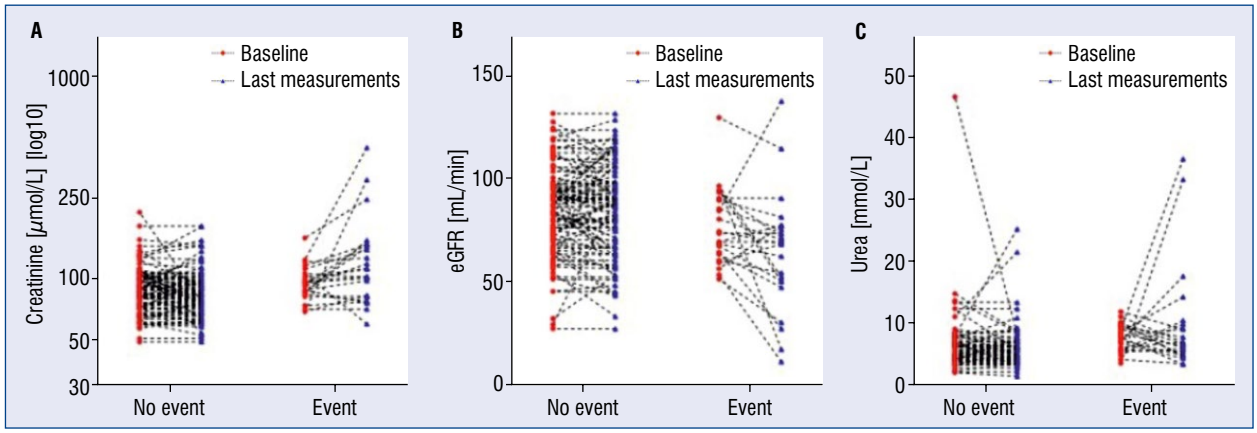

Figure 2. A. Change in creatinine over time. Paired dot plot charts representing baseline creatinine measurements (red dots) and last available creatinine measurements (blue dots) in patients without an event (left) and in patients reaching the endpoint (death or heart transplantation, right). Values for the same patient are connected via a dashed line. The y-axis is depicted in a log10-scale; **B.** Change in estimated glomerular filtration rate (eGFR) over time. Paired dot plot charts representing baseline eGFR measurements (red dots) and the last available eGFR measurements (blue dots) in patients without an event (left) and in patients reaching the endpoint (death or heart transplantation, right). Values from the same patient are connected via a dashed line; **C.** Change in urea over time. Paired dot plot charts representing baseline urea measurements (red dots) and last available urea measurements (blue dots) in patients without an event (left) and in patients reaching the endpoint (death or heart transplantation, right). Values from the same patient are connected via a dashed line.

Survival analysis

Cox regression analysis revealed a highly significant relationship between the creatinine level and the risk of death or heart transplantation. The risk of reaching the endpoint was substantially increased in both the unadjusted analysis (hazard ratio [HR] 1.9 for every increase of 30 μmol/L, 95% confidence interval [CI] 1.39–2.57, $p < 0.001$) and after adjustment for age and gender (adjusted HR 1.9, 95% CI 1.37–2.57, $p < 0.001$, Fig. 3A). Doubling of creatinine (log2 analysis) resulted in an almost 8 times higher risk of death or transplantation in both unadjusted analysis (HR 7.8, 95% CI 3.09–19.76, $p < 0.001$) and after adjustment for age and gender (adjusted HR 7.7, 95% CI 2.96–19.85, $p < 0.001$, Fig. 3B).

Similarly, for eGFR a highly significant relationship with the risk of death or heart transplantation was observed. The risk of reaching the endpoint was about twice as high with every 15 mL/ /min decrease in both the unadjusted analysis (HR 1.8, 95% CI 1.34–2.54, $p = 0.0002$) and after adjustment for age and gender (adjusted HR 1.9, 95% CI 1.36–3.62, $p = 0.0001$, Fig. 3A). Bisection of eGFR (log2 analysis) was associated with a 5 times higher risk of death or transplantation in both unadjusted analysis (HR 4.9, 95% CI 2.30–10.52, $p = 0.0002$) and after adjustment for age and gender (adjusted HR 5.3, 95% CI 2.40–11.60, $p < 0.0001$, Fig. 3B).

In addition, the prognostic relevance of clinically used cut-off values was assessed. An eGFR ≤ 60 mL/min was associated with a 4 times higher risk of death or transplantation in both the unadjusted analysis (HR 3.9, 95% CI 1.5–10, $p = 0.005$) and after adjustment for age and gender (adjusted HR 4.0, 95% CI 1.55–10.6, $p = 0.004$, Fig. 3C). An even stronger effect was observed for an eGFR ≤ 30 mL/min with an 8 to 10 times higher risk in the unadjusted analysis (HR 8.2, 95% CI 2.34–28.4, $p = 0.001$) and after adjustment for age and gender (adjusted HR 10.5, 95% CI 2.87–38.2, $p = 0.0004$, Fig. 3C).

Comparably, a highly significant relationship between urea levels and the risk of death or heart transplantation was seen. The risk of reaching the endpoint was increased with higher urea in both the unadjusted analysis (HR 1.6 for every increase of 5 mmol/L, 95% CI 1.15–2.16, $p = 0.005$) and after adjustment for age and gender (adjusted HR 1.6 for every increase of 5 mmol/L, 95% CI 1.15–2.19, $p = 0.004$, Fig. 3A). Doubling of urea (log2 analysis) resulted in an increased risk of death or transplantation by factor 2.5 in both the unadjusted analysis (HR 2.5, 95% CI 1.49–4.23, $p = 0.0006$) and after adjustment for age and gender (adjusted HR 2.5, 95% CI 1.50–4.32, $p = 0.0006$, Fig. 3B).

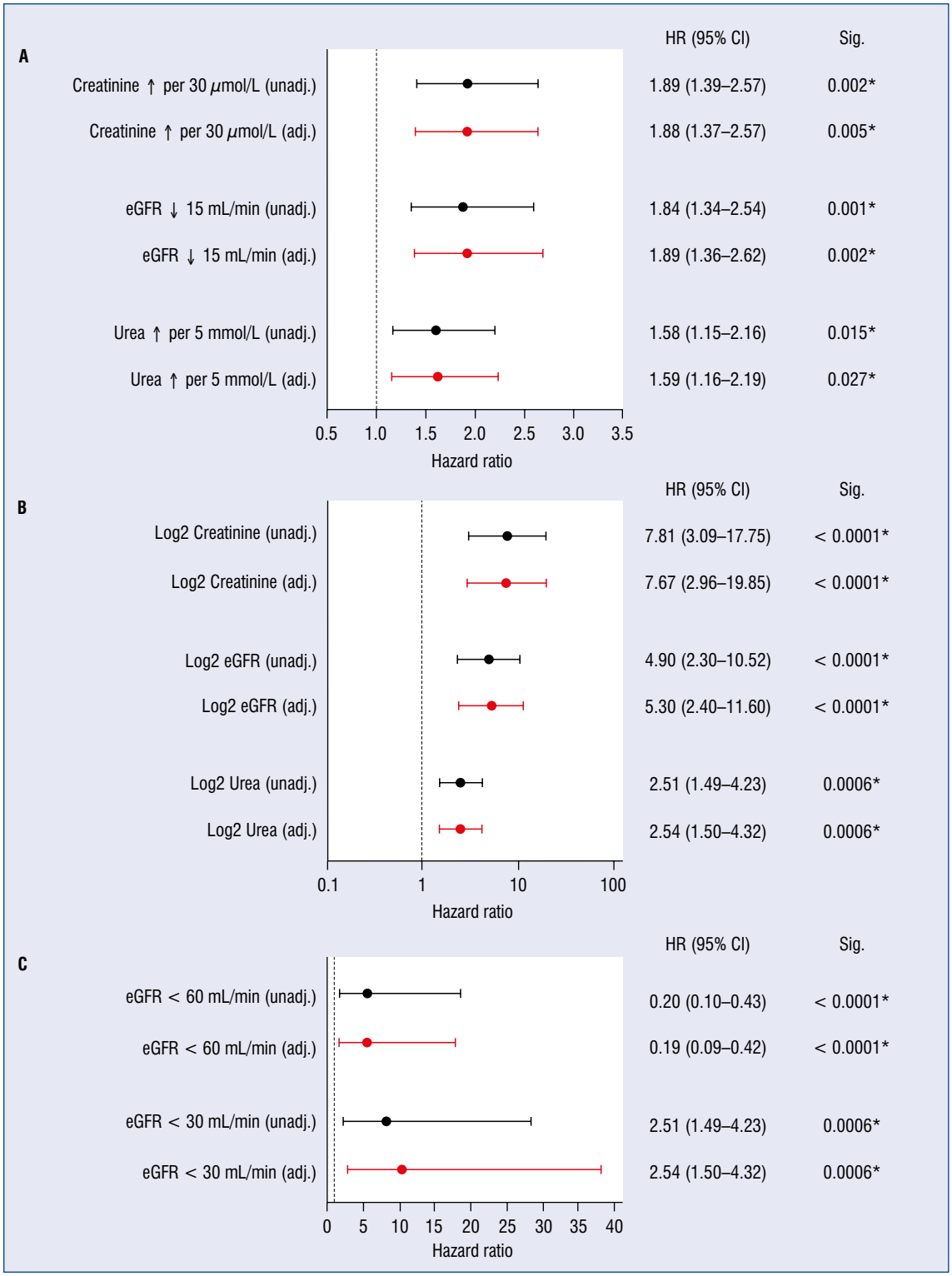

Figure 3. A. Hazard ratios (HR) of creatinine, estimated glomerular filtration rate (eGFR) and urea per interval increase in terms of death or heart transplantation. HR, unadjusted (unadj.) and adjusted (adj.) for age and gender, with 95% confidence intervals (CI) per 30 μmol/L increase in creatinine, 15 mL/min decrease in eGFR and 5 mmol/L increase in urea; **B.** Hazard ratios of creatinine, eGFR and urea per log2 change in terms of death or heart transplantation. HR, unadjusted and adjusted for age and gender, with 95% CI on a log10-scale per doubling of creatinine, bisection of eGFR and doubling of urea; **C.** Hazard ratios of different eGFR in terms of death or heart transplantation. HR, unadjusted and adjusted for age and gender, with 95% CI for eGFR < 60 mL/min and eGFR < 30 mL/min; *significant values ($p < 0.05$).

Additional analysis blanking older values

Owing to the retrospective study design the interval between the assessment of kidney function and the endpoint was variable (median distance [days] to event for creatinine/eGFR measurements 121 [IQR 6.0–370.5]; for urea 121 [IQR 6.0–370.5]). Therefore, an additional analysis was performed where all values were measured more than 1 year before an event were blanked. Also with this approach, results were consistent (**Suppl. Table S1**). For eGFR ≤ 30 mL/min it was no longer possible to calculate HRs due to complete separation (empty cells as a result of fewer data points).

Discussion

Predictors of mortality remain scarce in patients with LVNC. Renal dysfunction is common in patients with heart disease, occurring due to individual combinations of pre-existing renal damage, impaired perfusion, and venous congestion [28]. Impaired renal function has been observed to predict poor outcome in various cardiomyopathies [16–18]. This study determined the prognostic value of renal function in one of the largest LVNC cohorts published to date, with 126 patients and a median follow-up duration of more than 7.9 years. The overall mortality and heart transplantation rate was 18%, which is in the range of previous studies reporting rates were between 2% and 35% [7, 29–32].

Kidney function was a strong predictor of death or heart transplantation in LVNC patients. Elevated creatinine was associated with a substantially higher risk of death or heart transplantation in our cohort. Doubling of creatinine resulted in an almost 8 times higher risk of death or transplantation. Since creatinine is freely filtered by the glomerulus, it allows direct estimation of GFR in some cases. However, multiple sources of bias (such as age and gender) lead to an inaccurate estimation of GFR [33]. Therefore, in the present study the CKD-EPI formula was used, which includes age, race, and serum creatinine and estimates GFR more accurately in patients with chronic systolic heart failure compared with the MDRD or Cockcroft-Gault equation [34]. Every bisection of kidney function assessed by eGFR was associated with a 5-times higher risk. An even 8 to 10 times higher risk was observed for patients with an eGFR of less than 30 mL/min. Similar associations of impaired kidney function and clinical outcome have been documented for other cardiomyopathies. In non-ischemic dilated cardiomyopathy, an eGFR < 60 mL/min was an independent predictor of death or the need for heart transplantation [17]. A very similar relationship was described in children with dilated cardiomyopathy [16]. In patients with takotsubo cardiomyopathy, lower eGFR values during hospitalization were associated with longer hospitalizations and higher rates of adverse events [18]. These findings suggest that the cardio-renal association is similar in LVNC and other cardiomyopathies. Heart failure interacts with kidney function via numerous pathways in both an acute and chronic setting. This complex interplay involves hemodynamic, (neuro-)humoral, and direct cardiovascular disease-associated mechanisms [35]. A possible reason why eGFR is such a powerful and consistent predictor of outcome in different heart diseases is its dependency on renal perfusion and thus on cardiac output [36–38].

In line with the described findings for creatinine, elevated urea was associated with a higher risk of death and heart transplantation. Doubling of urea resulted in a 2.5-times increased risk. In acute heart failure patients, it was even observed to be the strongest predictor of mortality amongst all renal function parameters [39]. Possibly, this is due to the fact that urea is not only dependent on renal perfusion, but also on tubular function (up to 50% of urea is passively reabsorbed in the renal tubules) and is closely related to neurohumoral activity such as renin–angiotensin–aldosterone system activity [40]. Thus, compared with creatinine, urea may be more sensitive to changes in diuretic therapy, venous congestion and volume status.

Limitations of the study

Even though this was one of the largest LVNC cohorts studied, this cardiomyopathy is still rare and thus conclusions are limited by the relatively small number of events. Further on, referral bias, and — given the observational retrospective study design — possible confounding bias as well as missing measurements of patients not requiring medical care may have affected the results.

Conclusions

This study provides evidence that a decrease in kidney function as assessed by creatinine, eGFR, and urea is associated with an increased risk of death and heart transplantation in patients with LVNC. In light of this observation, it is suggested herein, that renal function should be included in follow-up and risk assessment of LVNC patients.

Conflict of interest: No specific funding has been used for this project. Richard Kobza has received institutional grants from Abbott, Biosense-Webster, Biotronik, Boston, Medtronic, Sis-Medical and consulting fees from Biosense-Webster and Biotronik. Simon F. Stämpfli has received speaker and consulting fees from Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Fumedica, Novartis, Pfizer, and Takeda. Other authors report no conflict of interest.

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