Journal of the American Heart Association

ORIGINAL RESEARCH

Role of Heart Rate Variability in Association Between Glomerular Hyperfiltration and All-Cause Mortality

Hao-Chih Chang, MD; Chi-Jung Huang, PhD; Albert C. Yang, MD, PhD; Hao-Min Cheng, MD, PhD; Shao-Yuan Chuang, PhD; Wen-Chung Yu, MD; Chern-En Chiang, MD; Chen-Huan Chen, MD; Shih-Hsien Sung, MD, PhD

BACKGROUND: Glomerular hyperfiltration (GHF) is paradoxically associated with increased cardiovascular events in healthy individuals, but the pathogenesis remains unclear. We aim to investigate whether GHF is associated with mortality and whether decreased heart rate variability (HRV) is associated with GHF.

METHODS AND RESULTS: We retrospectively analyzed 1615 participants (aged 66.1±17.3 years, 61.9% men) without prior cardiovascular events. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. GHF was defined as glomerular filtration rate >the 95th percentile after stratification for age and sex, whereas normal filtration was defined as the 25th to 75th percentiles. HRV indexes, including time domain, frequency domain, and sample entropy, were measured using 24-hour ambulatory electrocardiography. Clinical outcomes were defined as all-cause mortality at 2 years. During a mean follow-up of 16.5±8.2 months, there were 117 deaths (7.2%). GHF was associated with a higher risk of death (hazard ratio and 95% CIs, 1.97 [1.15–3.37]). Reduced HRV indexes, including time domain, frequency domain, and sample entropy (odds ratio and 95% CIs, 0.79 [0.70–0.89]) were all independently associated with the presence of GHF after accounting for age, sex, mean heart rate, morbidities, and medications. In subgroup analysis, reduced HRV was more predictive of GHF in the young than the elderly. Mediation analysis revealed a significant mediation effect between HRV and GHF in addition to their respective detrimental effects on survival.

CONCLUSIONS: Reduced HRV was independently associated with the presence of GHF. Autonomic dysfunction may be involved in the pathogenesis of adverse outcomes of GHF in individuals without prior cardiovascular events.

Key Words: autonomic dysfunction ■ glomerular hemodynamics ■ glomerular hyperfiltration ■ heart rate variability ■ prognosis

Impaired renal function is a well-recognized risk factor for cardiovascular events (CVEs) and mortality, and the hazard increases sharply in patients with chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m^2.[1] Recently, it has been proposed that individuals with abnormally elevated eGFR, or glomerular hyperfiltration (GHF), are associated with adverse clinical outcomes.[2,3] In a multiethnic population consisting predominantly of patients who were hypertensive, Reboldi et al reported a U-shaped relationship between eGFR and adverse events, suggesting that GHF is an independent predictor of CVEs.[4] Dupuis et al also found that GHF was correlated with a higher risk of CVEs in patients who had chronic kidney disease stage 3a (eGFR 45–60 mL/min per 1.73 m^2) in a cohort of 9515 healthy participants.[5] Despite the fact that GHF may represent altered renal hemodynamics resulting from unfavorable neurohormonal activation,[6,7] the pathogenesis of the poor outcomes remains unclear.

Impaired cardiac autonomic function, which is prevalent in patients with chronic kidney disease,[8,9] has been

Correspondence to: Shih-Hsien Sung, MD, PhD, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shi-Pai Road, Beitou District, Taipei 112, Taiwan. E-mail: mr.sungsh@gmail.com

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Glomerular hyperfiltration (GHF) is paradoxically an established predictor of mortality in patients without prior cardiovascular events.
- Reduced heart rate variability, assessed by 24-hour ambulatory electrocardiography, is significantly associated with the presence of GHF, especially in younger patients.
- There is a significant mediation effect between heart rate variability and GHF, suggesting a reinforcement mechanism contributing toward the detrimental consequences on clinical outcomes.

What Are the Clinical Implications?

- Heart rate variability, a surrogate of cardiac autonomic activity that is easily accessible in clinical practice, can be reflective of the unfavorable neurohormonal milieu underlying GHF.
- This study unveils the pathogenesis of GHF and sparks future research to identify early, noninvasive markers for mortality and to evaluate the mechanisms linking the renin-angiotensin-aldosterone system with hyperfiltration-associated cardiovascular risk.

Nonstandard Abbreviations and Acronyms

CVE	cardiovascular event
GHF	glomerular hyperfiltration
HF	high-frequency power
HRV	heart rate variability
LF	low-frequency power
pNN20	percent of the interbeat intervals differing from neighboring intervals by >20 ms
RAS	renin-angiotensin-aldosterone system
SDANN	SD of the 5-minute average normal interbeat intervals
SDNN	SD of the normal interbeat intervals
VLF	very-low-frequency power

associated with a poor prognosis.[10] Previous studies have described the association between adrenergic tone and the maladaptive activation of the renin-angiotensin-aldosterone system (RAS).[11] Through preferential increase in efferent resistance of the glomeruli, the maladaptive RAS may subsequently contribute to the changes in glomerular hemodynamics.[12,13] Heart rate variability (HRV), a noninvasive surrogate characterizing the modulation of autonomic tone, is associated with the prognosis of cardiovascular diseases beyond traditional cardiovascular risk factors.[14,15] It has been reported that reduced HRV is independently associated with the activated RAS in patients who are hypertensive.[16,17] However, no study has evaluated the association between autonomic function and the presence of GHF. Therefore, the objectives of this study were to investigate whether GHF is associated with mortality and whether decreased HRV is associated with GHF and mortality in apparently healthy participants.

METHODS

Study Population

The study population was drawn from an intramural registry of Taipei Veterans General Hospital (TARGET registry)[18,19] and enrolled patients from June 2009 to December 2012 for the surveys conducted on cardiovascular diseases. Medical history, physical examination findings, prescribed medications, and biochemical examinations were prospectively logged in a web-based electronic medical recording system. Participants who had undergone comprehensive echocardiographic studies, 24-hour ambulatory ECG monitoring, and blood tests for biochemistry within a month were eligible. Patients with prior CVEs, including heart failure, myocardial infarction, stroke, or transient ischemic attack, and those with arrhythmia, sick sinus syndrome, or pacing rhythm or those who used β-blockers were excluded. In this study, hypertension was defined as an office systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥80 mm Hg or currently on antihypertensive treatment. Coronary artery disease (CAD) was diagnosed using coronary angiograms with ≥50% luminal reduction of ≥1 coronary arteries. The investigation conformed to the principles outlined in the Declaration of Helsinki, and the Institutional Review Board of Taipei Veterans General Hospital approved the study and waived the requirement for informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Definition of GHF

eGFR was calculated using serum creatinine measured within 30 days of ECG studies using the Chronic Kidney Disease Epidemiology Collaboration equation,

$$\text{eGFR} = 141 \times min\left(\frac{\text{Scr}}{\kappa}, 1\right)^{\alpha} \times max\left(\frac{\text{Scr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{age}} \times 1.018\ (\text{if female})$$

where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min indicates the minimum value of Scr/κ or 1, and max indicates the maximum value of Scr/κ or 1.[20] The sex-specific distributions of Chronic Kidney Disease Epidemiology Collaboration–calculated eGFR were divided by age decades. GHF was defined as an eGFR >95th percentile (or 2 SDs above the mean), whereas a normal filtration rate was defined as an eGFR between the 25th and 75th percentiles, and a low filtration rate was defined as an eGFR <5th percentile, after stratification for age decades and sex.

Measurements of HRV

The 24-hour ambulatory ECG monitoring was performed using a 3-channel digital recorder (Medilog FD4, Oxford Instruments, UK). When >18 hours of good quality ECG signals were obtained, the stored signals were then automatically processed using open-source HRV algorithms, as was done in our previous studies.[19,21] The R-R intervals between ectopic beats, normal and ectopic beats, and unrecognizable beats were excluded from the analysis. Patients with rejected intervals of >5% were also excluded. In brief, time-domain measures of HRV consisted of mean heart rate and SD of the normal interbeat intervals (SDNN), the SD of the 5-minute average normal interbeat intervals (SDANN), the root mean square of the successive difference between adjacent normal interbeat intervals, and the percentage of adjacent intervals that varied by >20 ms (pNN20). Spectral HRV measures included high-frequency power (HF; 0.15–0.40 Hz), low-frequency power (LF; 0.04–0.15 Hz), and very-low-frequency power (VLF; 0.003–0.04 Hz). A natural logarithmic transformation was used to normalize the distribution of the spectral HRV measurements. Sample entropy, a nonlinear processing approach, was also measured to quantify the complexity and regularity of the heart rate time series.[22]

Outcomes Measure

Clinical outcomes and mortality were acquired by linking the database to the National Death Registry 2 years after enrollment. The National Death Registry database registers valid information according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*). The *ICD-9* codes for cardiovascular deaths ranged from 390 to 459. The accuracy of the coding in Taiwan's National Death Registry database has been validated.[23]

Statistical Analysis

Baseline characteristics are reported as mean±SD for continuous variables and percentages for categorical variables. One-way ANOVAs were conducted to evaluate the differences in baseline characteristics and HRV parameters between the low, normal, and high filtration groups. Post hoc analysis with the Bonferroni test was performed for between-group comparisons. Kaplan–Meier survival curve analysis was conducted to reveal the trend of prognosis between the low, normal, and high glomerular filtration groups. Cox proportional hazards regression models were used to evaluate the independence of HRV variables and the presence of GHF in the prediction of 2-year all-cause mortality. Logistic regression analysis was used to evaluate the association between HRV and the existence of GHF after adjusting for the covariates known to affect the eGFR. To explore the associations between HRV, GHF, and clinical outcome, we conducted mediation analysis. Single-mediator analyses, with either HRV or GHF as the mediator, were used to assess the direct and indirect effects on the time-to-event outcomes under the Cox proportional hazards models.[24] To assess the robustness of the mediation analysis to unmeasured confounding for total effects, we computed the E-value as a sensitivity analysis to estimate the strength of the confounder–outcome relationship and the approximate strength of the confounder–mediator relationship.[25,26] Statistical significance was set at $P<0.05$. All statistical analyses were performed using SPSS version 22.0 (International Business Machines Corporation, Chicago, IL) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics and HRV

A total of 1615 participants (aged 66.1±17.3 years, 61.9% men) were analyzed (Figure 1). Among them, 778 (48.2%) participants had hypertension, 307 (19.0%) had diabetes, and 296 (18.3%) had CAD. According to the age-specific and sex-specific percentiles of eGFR distributions, we categorized the participants as having low filtration (n=90 [5.5%]), normal filtration (n=959 [59.4%]), and high filtration (N=130 [8%]). The baseline characteristics of the 3 groups are shown in Table 1. In brief, the low filtration group had the lowest levels of hemoglobin, albumin, and high-density lipoprotein cholesterol; highest levels of serum creatinine and glucose; and highest prevalence of hypertension, diabetes, and CAD and use of calcium channel blockers or diuretics. There was no significant between-group difference between the high and normal filtration groups except for lower hemoglobin levels and less prescribed statins in the high filtration group. Regarding HRV indexes, SDNN, SDANN, pNN20, VLF power, LF power, HF power, total power, and sample entropy were significantly higher in the normal filtration group than

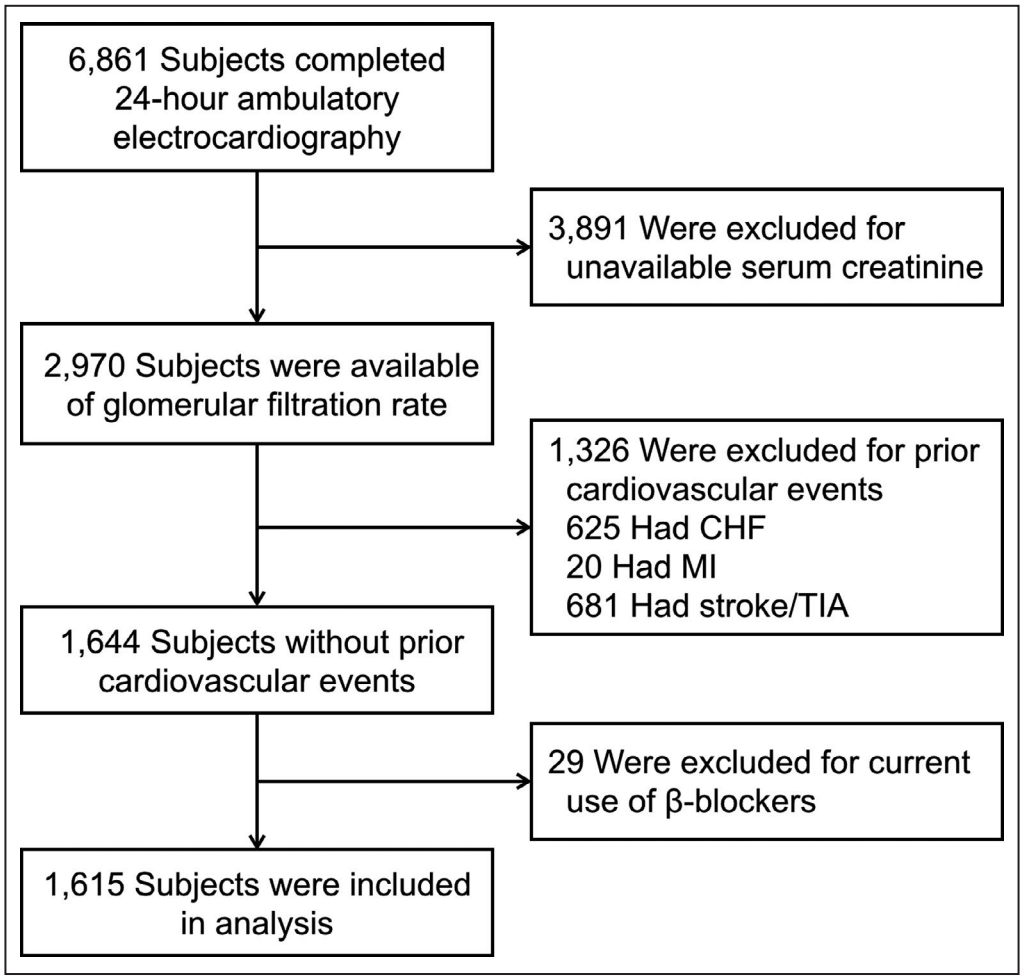


Figure 1. Flowchart of the study population.
CHF indicates congestive heart failure; MI, myocardial infarction; and TIA, transient ischemic attack.

those in the other 2 groups, whereas there was no significant difference in any of the HRV indexes between the high and low filtration groups (Table 2). The root mean square of the successive difference between adjacent normal interbeat intervals was similar between the 3 groups.

Follow-Up and Survival Analysis

During a mean follow-up of 16.5±8.2 months, there were 117 deaths (7.2% of the study population). Figure 2 shows the 2-year survival curves stratified by filtration group. Participants with either low (hazard ratio [HR], 3.18; 95% CI, 1.43–7.08) or high filtration rates were associated with higher mortality than those with a normal filtration rate (HR, 3.20; 95% CI, 1.61–6.38).

Among the participants with either normal or high glomerular filtration rates, the presence of GHF was independently correlated with an increased risk of all-cause death (HR, 2.92; 95% CI, 1.74–4.90) after adjusting for age, sex, and mean heart rate in the multivariate Cox proportional hazards regression model (Table 3, model 1). The association remained true (HR, 1.97; 95% CI, 1.15–3.37) when hemoglobin, diabetes, and the use of statins were further accounted for (Table 3, model 2).

In addition, both the time-domain (SDNN, SDANN, pNN20) and frequency-domain HRV indexes (VLF power, LF power, HF power, and total power) as well as sample entropy were all independently related to mortality at 2 years after adjusting for age, sex, and mean heart rate (Table 3, model 1). When hemoglobin, diabetes, and the use of statins were further accounted for, the frequency-domain HRV indexes (VLF power, LF power, and total power) and sample entropy remained the independent predictors of poor prognosis (Table 3, model 2).

Predictors of GHF

Among the participants with either normal or high glomerular filtration rates, SDNN, SDANN, pNN20, VLF power, LF power, HF power, total power, and sample entropy were all inversely predictive of GHF. After adjusting for age, sex, and mean heart rate,

Table 1. Baseline Characteristics Between Low, Normal, and High Glomerular Filtration

Variables	Low (<5th), n=90	Normal (25th–75th), n=959	High (>95th), n=130	*P* value
Age, y	65.9±17.1	65.3±17.3	67.0±19.4	0.585
Male sex	50 (55.6)	602 (62.8)	71 (54.6)	0.101
Systolic BP, mm Hg	128.8±22.3	126.8±19.7	121.8±21.1	0.070
Diastolic BP, mm Hg	70.2±13.8	72.6±12.6	70.1±12.1	0.144
Laboratory testing				
Hemoglobin, g/dL	10.3±1.9	12.7±2.0*	12.0±1.9*,†	<0.001
Creatinine, mg/dL	4.6±2.9	0.9±0.2*	0.6±0.2*,†	<0.001
eGFR, mL/min per 1.73 m^2	20.9±21.8	80.2±20.6*	102.0±21.1*,†	<0.001
Albumin, mg/dL	3.6±0.6	3.9±0.5*	3.8±0.6	<0.001
Glucose, mg/dL	134.9±71.5	108.9±47.3*	118.2±55.6	0.001
LDL-c, mg/dL	104.0±39.7	113.0±34.9	111.3±35.0	0.040
HDL-c, mg/dL	42.6±14.5	49.4±15.6*	50.4±16.6	0.031
Echocardiography				
LVEF, %	62.7±7.5	60.2±5.9*	61.1±6.0	0.031
E/A ratio	0.9±0.4	1.0±0.5	1.0±0.5	0.338
Medial E/e'	6.4±1.1	4.5±0.2*	4.6±0.6	0.006
RVSP, mm Hg	38.7±17.9	30.2±9.6*	32.3±10.5*	<0.001
Comorbidities				
Hypertension	56 (62.2)	431 (44.9)*	50 (38.5)*	0.002
Diabetes	34 (37.8)	147 (15.3)*	17 (13.1)*	<0.001
CAD	29 (32.2)	169 (17.6)*	17 (13.1)*	0.001
Medications				
RAS inhibitor	0 (0)	10 (1.0)	4 (4.4)*	0.007
CCB	36 (40)	286 (29.8)*	31 (23.8)*	0.036
Diuretics	23 (25.6)	116 (12.1)*	19 (14.6)*	0.001
Aspirin	23 (25.6)	228 (23.8)	24 (18.5)	0.354
Statins	14 (15.6)	153 (16.0)	10 (7.7)*,†	0.046

Data are provided as mean±SD or number (percentage). BP indicates blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin-aldosterone system; and RVSP, right ventricular systolic pressure.

*P<0.01 vs the low filtration group.

†P<0.01 vs the normal filtration group.

the correlations between HRV indexes and GHF remained (Table 4, model 1). With further adjustments for known factors affecting glomerular filtration, including the presence of hypertension, diabetes, and the use of RAS inhibitors (Table 4, model 2), SDNN, SDANN, pNN20, VLF power, LF power, HF power, total power, and sample entropy were still independently correlated with GHF. In the stratified analysis, reduced sample entropy was related to the presence of GHF, regardless of age, sex, hypertension, diabetes, or CAD (Figure 3). However, the association between sample entropy and GHF was more prominent in participants aged ≤65 years than those aged >65 years.

Mediation Analysis

Figure 4A presents the mediation effect of GHF between HRV and mortality, whereas Figure 4B demonstrates the mediation effect of HRV between GHF and mortality. In the model using total power as the measure of HRV, we found that total power had a direct effect on mortality (adjusted HR, 0.71; 95% CI, 0.59–0.86; E-value=2.15), and the effect could be mediated through the pathway of GHF (adjusted HR, 0.95; 95% CI, 0.93–0.98; E-value=1.28). In contrast, GHF was directly associated with an increased risk for mortality (adjusted HR, 2.81; 95% CI, 1.68–4.70; E-value=5.07; Figure 4B), which could be mediated by the reduced total power (adjusted HR, 1.12; 95% CI, 1.03–1.22; E-value=1.48). The results were consistent while using sample entropy as the measure of HRV (Figure 4A and 4B, right). In brief, the presence of GHF explained 10.5% and 7.7% of the detrimental effects of reduced low total power and sample entropy on survival, respectively, whereas reduced total power and

Table 2. Heart Rate and HRV in Patients With Low, Normal, and High Glomerular Filtration

Variables	Low (<5th), n=90	Normal (25th–75th), n=959	High (>95th), n=130	*P* value
Heart rate, bpm	85.4±16.3	82.8±15.4	87.7±18.5*	0.002
Time domain				
SDNN, ms	89.9±44.9	104.5±36.9†	87.5±37.9*	<0.001
SDANN, ms	75.5±41.5	89.7±35.0†	73.7±33.1*	<0.001
RMSSD, ms	38.5±29.6	37.0±24.1	33.6±25.6	0.264
pNN20, %	30.8±23.3	37.8±19.7†	31.9±22.0*	<0.001
Frequency domain				
Ln VLF	7.5±1.2	8.2±0.8†	7.8±1.1*	<0.001
Ln LF	6.3±1.5	6.8±1.0†	6.3±1.2*	<0.001
Ln HF	6.3±1.5	6.4±1.3	6.1±1.5*	0.005
Ln TP	8.1±1.2	8.6±0.8†	8.2±1.1*	<0.001
Nonlinear analyses				
Sample entropy	1.6±0.2	1.7±0.1†	1.6±0.2*	<0.001

Data are provided as mean±SD. HF indicates high-frequency power; HRV, heart rate variability; LF, low-frequency power; Ln, natural logarithm; pNN20, percent of the interbeat intervals differing from neighboring intervals by >20 ms; RMSSD, root mean square of the successive difference between adjacent normal interbeat intervals; SDANN, SD of the 5-minute average normal interbeat intervals; SDNN, SD of the normal interbeat intervals; TP, total power of heart rate variability power spectrum; and VLF, very-low-frequency power.

*$P<0.01$ vs the normal filtration group.

†$P<0.01$ vs the low filtration group.

sample entropy mediated 15.6% and 18% of the effect of GHF on all-cause mortality.

DISCUSSION

The present study is the first to demonstrate that patients with GHF have impaired HRV with regard to time-domain and frequency-domain indexes and entropy compared with those with normal filtration rates. Similar to those with impaired renal function, patients with GHF was also associated with poor survival. In addition, impaired HRV was independently predictive of GHF after adjusting for age, sex, heart rate, and other confounders. The relationship between HRV and GHF consistently existed in various subgroups, especially in the young participants rather than in the elderly. Mediation analysis further revealed a significant mediation effect between reduced HRV and GHF in addition to their detrimental consequences on clinical outcomes in apparently healthy individuals without prior CVEs (Figure 5).

Definition of GHF

It has been reported in multiple studies that GHF is associated with various medical conditions, such as pregnancy, hypertension, diabetes, or obesity.[27,28] However, there is no commonly established definition of GHF. Among the equations for estimating GFR, both the Modification of Diet in Renal Disease Study equation and Cockcroft-Gault formula may underestimate GFR, especially at higher levels, thus compromising their use in healthy individuals or patients with incipient kidney diseases with hyperfiltration.[29,30] To assess renal function in the general populations, GFR estimated from the Chronic Kidney Disease Epidemiology Collaboration equation may be more accurate, and it has been broadly used for defining GHF in previous studies.[20] However, using arbitrarily defined cutoff values for the definition of GHF may introduce bias regarding age-related or sex-related changes in eGFR.[29,31] Despite the lack of a guideline-established definition for GHF, an epidemiology-derived threshold for GHF after stratification for age and sex has been suggested and adopted in recent studies.[4,5,29] Therefore, we used the 95th percentile (or >2 SDs above the mean) of each age decade and sex as the threshold for GHF in the present study.

GHF and Clinical Outcomes

The pathologic role of supraphysiologic elevation in GFR has gained much interest during the past decade. Although hyperfiltration was shown to correlate with incipient loss of renal function in patients with diabetes, Tonelli et al further reported a U-shaped relationship between mortality and eGFR in an outpatient population of 1 526 437 patients.[32] In a pooled analysis of 8 prospective cohorts consisting predominantly of individuals who were hypertensive, GHF was a strong and independent predictor of CVEs.[4] In addition, Dupuis et al have demonstrated that GHF is also related to increased cardiovascular risks in healthy participants.[5] Although GHF is associated with worse cardiovascular

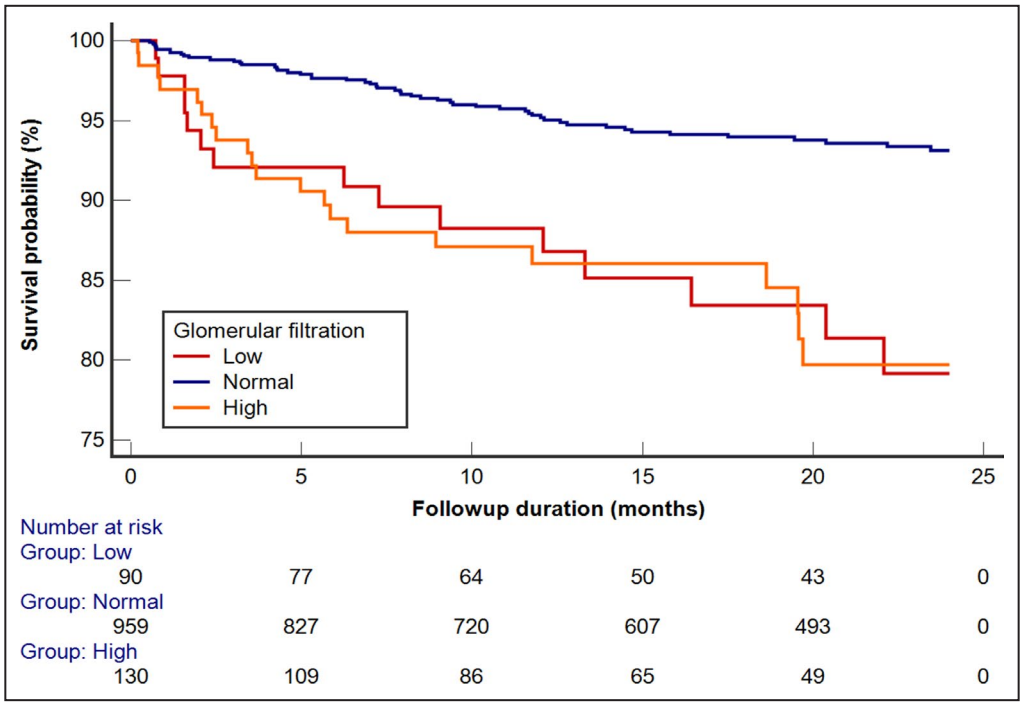


Figure 2. Kaplan–Meier survival curves for 2-year all-cause mortality, stratified by glomerular filtration groups.

prognosis, its clinical implications could be limited by the unclarified underlying mechanisms.

The present study demonstrated independent associations between HRV indexes and the presence of GHF, which suggest that autonomic dysfunction may be involved in the pathogenesis of the poor outcomes of GHF. Although it has already been established that an imbalance of the RAS results in altered glomerular

Table 3. Cox Proportional Hazards Regression Analysis Assessing the Association Between GHF, HRV, and 2-Year All-Cause Mortality

Variable	Model 1*		Model 2†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* value
GHF	2.922 (1.744–4.895)	<0.001	1.965 (1.145–3.370)	0.014
Time domain				
SDNN (1 SD=35.9 ms)	0.677 (0.540–0.848)	0.001	0.838 (0.650–1.079)	0.170
SDANN (1 SD=34.2 ms)	0.693 (0.550–0.873)	0.002	0.856 (0.656–1.116)	0.251
RMSSD (1 SD=22.7 ms)	0.909 (0.761–1.087)	0.296	0.951 (0.779–1.161)	0.621
pNN20 (1 SD=19.0%)	0.797 (0.669–0.950)	0.011	0.874 (0.717–1.066)	0.185
Frequency domain				
Ln VLF (1 SD=0.8)	0.709 (0.620–0.811)	<0.001	0.797 (0.688–0.923)	0.002
Ln LF (1 SD=1.0)	0.707 (0.606–0.824)	<0.001	0.796 (0.671–0.945)	0.009
Ln HF (1 SD=1.2)	0.810 (0.692–0.947)	0.008	0.876 (0.735–1.044)	0.138
Ln TP (1 SD=0.8)	0.726 (0.627–0.840)	<0.001	0.808 (0.688–0.949)	0.009
Nonlinear analyses				
Sample entropy (1 SD=0.1)	0.824 (0.764–0.890)	<0.001	0.856 (0.778–0.942)	0.001

GHF indicates glomerular hyperfiltration; HF, high-frequency power; HR, hazard ratio; HRV, heart rate variability; LF, low-frequency power; Ln, natural logarithm; pNN20, percent of the interbeat intervals differing from neighboring intervals by >20 ms; RMSSD, root mean square of the successive difference between adjacent normal interbeat intervals; SDANN, SD of the 5-minute average normal interbeat intervals; SDNN, SD of the normal interbeat intervals; TP, total power of HRV power spectrum; and VLF, very-low-frequency power.

*Adjusting for age, sex, and heart rate.

†Adjusting for age, sex, mean heart rate, hemoglobin, diabetes, and the use of statin.

Table 4. Logistic Regression Analysis of the Association Between HRV (Per 1 SD) and the Existence of Glomerular Hyperfiltration

Variables	Model 1*		Model 2†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Time domain				
SDNN (1 SD=35.9 ms)	0.662 (0.521–0.841)	0.001	0.655 (0.514–0.834)	0.001
SDANN (1 SD=34.2 ms)	0.655 (0.514–0.836)	0.001	0.655 (0.513–0.836)	0.001
RMSSD (1 SD=22.7 ms)	0.903 (0.743–1.097)	0.303	0.891 (0.733–1.083)	0.247
pNN20 (1 SD=19.0%)	0.802 (0.666–0.966)	0.020	0.792 (0.657–0.956)	0.015
Frequency domain				
Ln VLF (1 SD=0.8)	0.750 (0.630–0.892)	0.001	0.741 (0.622–0.883)	0.001
Ln LF (1 SD=1.0)	0.741 (0.620–0.885)	0.001	0.731 (0.611–0.874)	0.001
Ln HF (1 SD=1.2)	0.797 (0.672–0.886)	0.009	0.788 (0.663–0.936)	0.007
Ln TP (1 SD=0.8)	0.747 (0.630–0.886)	0.001	0.737 (0.620–0.875)	0.001
Nonlinear analyses				
Sample entropy (1 SD=0.1)	0.795 (0.709–0.891)	<0.001	0.790 (0.704–0.886)	<0.001

HF indicates high-frequency power; HRV, heart rate variability; LF, low-frequency power; Ln, natural logarithm; OR, odds ratio; pNN20, percent of the interbeat intervals differing from neighboring intervals by >20 ms; RAS, renin-angiotensin-aldosterone system; RMSSD, root mean square of the successive difference between adjacent normal interbeat intervals; SDANN, SD of the 5-minute average normal interbeat intervals; SDNN, SD of the normal interbeat intervals; TP, total power of HRV power spectrum; and VLF, very-low-frequency power.

*Adjusting for age, sex, and heart rate.

†Adjusting for age, sex, mean heart rate, hypertension, diabetes, and the use of RAS inhibitors.

hemodynamics,[27] sympathetic nerve activity, which may modulate the RAS, could therefore influence GFR.[33] In young participants with mild hypertension, Schmieder et al demonstrated the stress-induced sympathetic activation could provoke GHF, with a concomitant increase of angiotensin II.[34] Increased levels of angiotensin II may contribute to hyperfiltration via efferent arteriolar vasoconstriction, whereas blockade of the RAS may reverse the hyperfiltrating state.[7,35] In contrast, renal sympathetic denervation may prevent

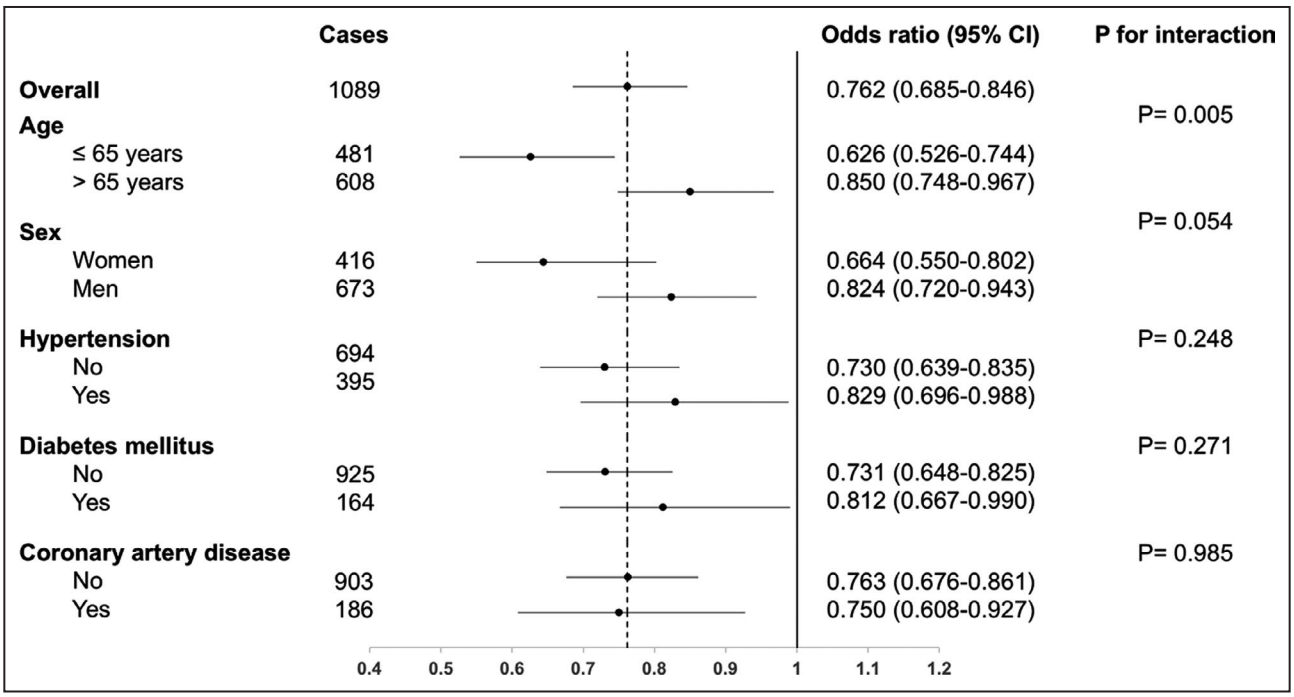
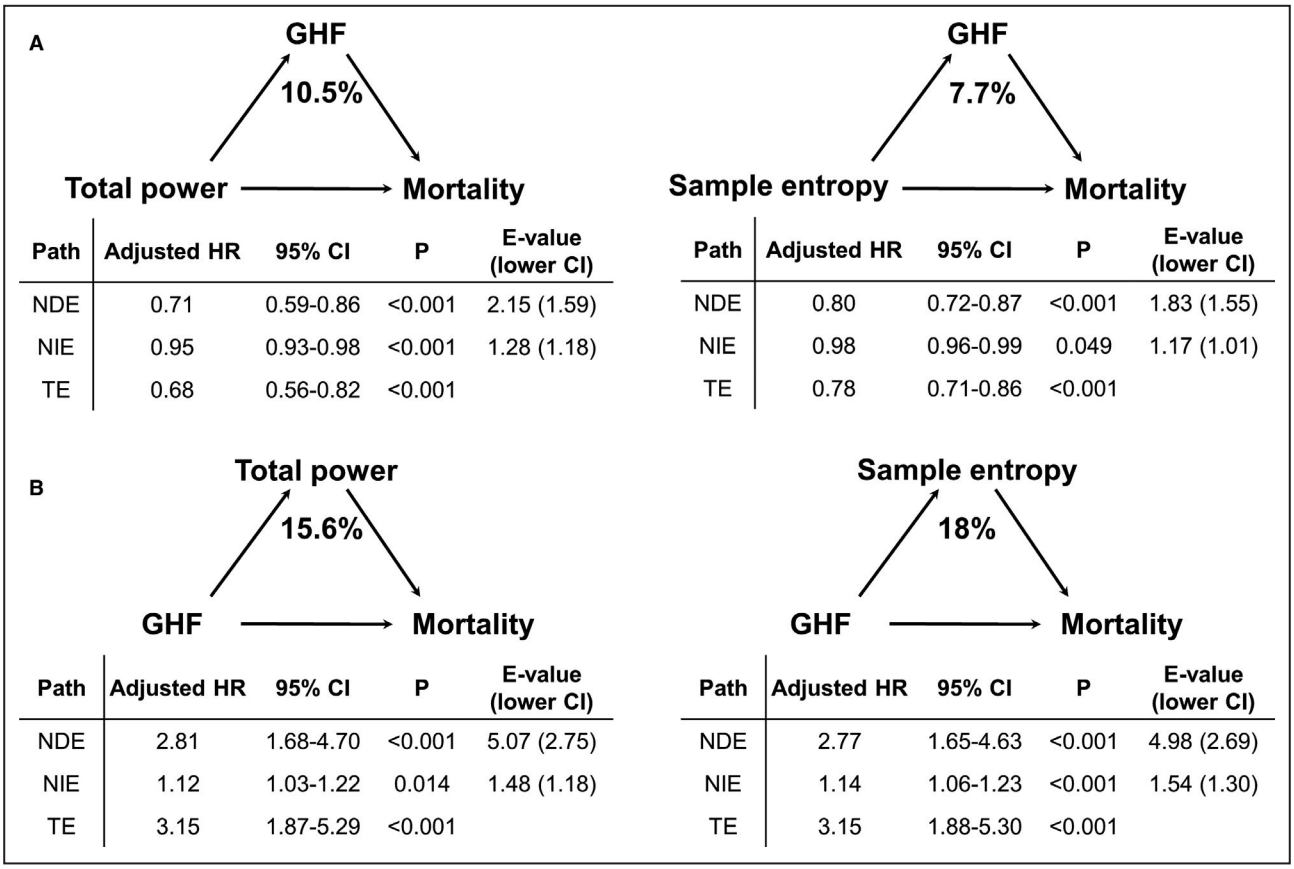


Figure 3. Odds ratio and 95% CIs per 1 SD increase of sample entropy (1 SD=0.1) of the heart rate variability for the presence of glomerular hyperfiltration in the younger (≤65 years) and older (>65 years) male and female patients and patients with and without hypertension, diabetes, or coronary artery disease or the use of the renin-angiotensin-aldosterone system inhibitors after controlling for age.



Path	Adjusted HR	95% CI	P	E-value (lower CI)
NDE	0.71	0.59-0.86	<0.001	2.15 (1.59)
NIE	0.95	0.93-0.98	<0.001	1.28 (1.18)
TE	0.68	0.56-0.82	<0.001	

Path	Adjusted HR	95% CI	P	E-value (lower CI)
NDE	0.80	0.72-0.87	<0.001	1.83 (1.55)
NIE	0.98	0.96-0.99	0.049	1.17 (1.01)
TE	0.78	0.71-0.86	<0.001	

Path	Adjusted HR	95% CI	P	E-value (lower CI)
NDE	2.81	1.68-4.70	<0.001	5.07 (2.75)
NIE	1.12	1.03-1.22	0.014	1.48 (1.18)
TE	3.15	1.87-5.29	<0.001	

Path	Adjusted HR	95% CI	P	E-value (lower CI)
NDE	2.77	1.65-4.63	<0.001	4.98 (2.69)
NIE	1.14	1.06-1.23	<0.001	1.54 (1.30)
TE	3.15	1.88-5.30	<0.001	

Figure 4. Mediation analysis to explore the associations between HRV, GHF, and all-cause mortality.
The effect estimates (HR) and 95% CIs are reported for all paths. Models were adjusted for age, sex, and the mean heart rate. **A**, Effect of reduced HRV on all-cause mortality mediated by GHF. **B**, Effect of the presence of GHF on all-cause mortality mediated by reduced HRV. GHF indicates glomerular hyperfiltration; HR, hazard ratio; HRV, heart rate variability; NDE, natural direct effect; NIE, natural indirect effect; and TE, total effect.

GHF in an animal model.[36] By mediation analysis, the study results may support the fact that increased sympathetic tone, manifested as reduced HRV, could be a contributing factor for GHF.

On the other hand, the renal afferent nerve has been related to elevated central sympathetic drive and subsequently alters global autonomic tone. In patients who were hypertensive, Hoogerwaard et al illustrated that renal sympathetic denervation induces a significant decrease in the LF/HF ratio, suggesting a lower sympathetic balance.[37] In a population-based longitudinal cohort of 4605 participants, renal dysfunction was found to precede the change in HRV.[38] Clinical studies have reported that renal dysfunction may alter autonomic function through impaired autonomic reflex, activation of renal afferents, RAS, and cardiovascular remodeling.[39] GHF, manifested as the incipient decline of renal function, could be a proactive cause of the autonomic dysfunction that follows.

The significant interactions of impaired HRV and GHF in the young, rather than elderly patients, as shown in our study, highlights the more prominent association between autonomic function and GHF in the younger population. Given that a higher cardiovascular risk of GHF was observed in middle-aged individuals, as shown by previous studies, the significant association between reduced HRV and GHF, especially in younger participants (age ≤65 years), exemplifies its possible underlying mechanism.[2,4,5] In contrast, the correlations between reduced HRV and GHF were similar in both men and women and in patients with and without hypertension, diabetes, or CAD.

Study Limitations

This study has several limitations. First, eGFR was estimated from a single measurement of serum creatinine within a median duration of 3 days from the HRV measurements. The lack of information about muscle mass may misclassify patients with muscle wasting as a case of GHF. However, because the hyperfiltration group had similar serum albumin levels as the normal group and the significant association was higher in younger patients,[40] sarcopenia may be less likely to be a confounding factor. To replicate our findings, we applied the Modification of Diet in Renal Disease equation to assess eGFR, and

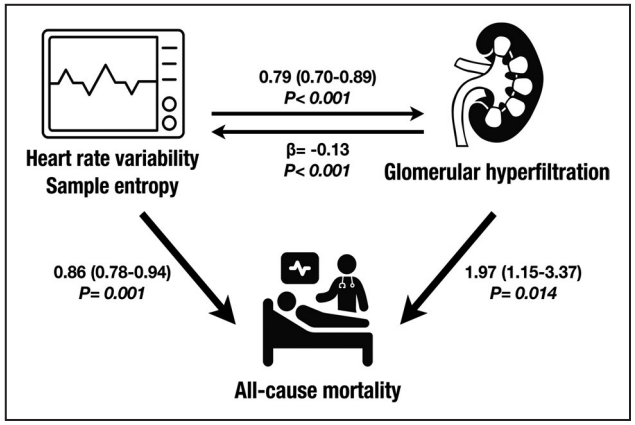


Figure 5. Association between heart rate variability, glomerular hyperfiltration, and all-cause mortality.
Glomerular hyperfiltration is paradoxically associated with a greater risk of cardiovascular events. There is a significant mediation effect between heart rate variability and glomerular hyperfiltration, suggesting a reinforcement mechanism contributing toward their respective detrimental consequences on clinical outcomes.

consistent results could be observed. Second, considering the poor agreement of the causes of death validated in the National Death Registry, only all-cause mortality was analyzed as the outcome in the present study. We were not able to attribute the diseases associated with HRV and GHF to cardiovascular or noncardiovascular deaths. In addition, we did not measure GFR repeatedly, and whether the death was related to the progressive decline of GFR or impaired HRV warrants prospective research. Third, HRV indexes are surrogates of global autonomic balance, as most of the parameters measure mixed autonomic influences from both sympathetic and parasympathetic activities rather than directly discern specific renal autonomic output. There is no single HRV parameter that can represent the renal sympathetic activity. However, HRV currently remains a noninvasive and simple tool for the assessment of autonomic activity in clinical practice. Finally, although we adjusted for the measured confounding factors, unmeasured confounding could still possibly influence the study findings.[25] However, our E-values suggested that considerable confounding would be needed to explain away the observed effect estimates, although modest confounding could explain the conservative estimates from CI closest to null. Further prospectively controlled studies with longitudinal follow-up are needed to validate the results, which can provide more solid evidence for causal inference.

GHF is an established predictor of premature death in patients without prior CVEs. The present study proposes a significant mediation effect between the reduced HRV and GHF on the long-term survival, suggesting a reinforcement mechanism contributing to their respective detrimental effect on the clinical outcomes. Because the unfavorable neurohormonal milieu has been identified as an independent cardiovascular risk factor for healthy individuals, the present study can spark future research to identify early, noninvasive markers for mortality, especially in young populations, and to evaluate the mechanisms linking the RAS with hyperfiltration-associated cardiovascular risks.

ARTICLE INFORMATION

Received March 11, 2021; accepted October 25, 2021.

Affiliations

Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (H.C., W.Y., S.S.); Department of Medicine, Taipei Veterans General Hospital Yuanshan and Suao Branch, Yilan, Taiwan (H.C.); Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan (H.C., H.C., W.Y., C.C., S.S.); Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (C.H., H.C.); Department of Internal Medicine (C.C., C.C., S.S.); and Institute of Public Health (C.C., S.S.), National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan; Digital Medicine Center and Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan (A.C.Y.); Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan (H.C., C.C.); Institute of Population Health Science, National Health Research Institutes, Miaoli, Taiwan (S.C.); and General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan (C.C.).

Sources of Funding

This study was supported by Taipei Veterans General Hospital (V104E12-003-MY3), Ministry of Science and Technology (MOST103-2314-B-010-050-MY2), and Ministry of Health and Welfare (MOHW107-TDU-B-211-123001, MOHW108-TDU-B-211-133001, MOHW109-TDU-B-211-114001), and the National Death Registry.

Disclosures

None.

REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305. doi: 10.1056/NEJMoa041031
2. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ. Renal hyperfiltration as a novel marker of all-cause mortality. *J Am Soc Nephrol*. 2015;26:1426–1433. doi: 10.1681/ASN.2014010115
3. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, Iseki K, Jassal SK, Kimm H, Kronenberg F, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ*. 2013;346:f324. doi: 10.1136/bmj.f324
4. Reboldi G, Verdecchia P, Fiorucci G, Beilin LJ, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Schwartz JE, et al. Glomerular hyperfiltration is a predictor of adverse cardiovascular outcomes. *Kidney Int*. 2018;93:195–203. doi: 10.1016/j.kint.2017.07.013
5. Dupuis ME, Nadeau-Fredette AC, Madore F, Agharazii M, Goupil R. Association of glomerular hyperfiltration and cardiovascular risk in middle-aged healthy individuals. *JAMA Netw Open*. 2020;3:e202377. doi: 10.1001/jamanetworkopen.2020.2377
6. Gorzelniak K, Engeli S, Janke J, Luft FC, Sharma AM. Hormonal regulation of the human adipose-tissue renin-angiotensin system: relationship to obesity and hypertension. *J Hypertens*. 2002;20:965–973. doi: 10.1097/00004872-200205000-00032
7. Ruster C, Wolf G. The role of the renin-angiotensin-aldosterone system in obesity-related renal diseases. *Semin Nephrol*. 2013;33:44–53. doi: 10.1016/j.semnephrol.2012.12.002
8. Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, Coresh J. Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol*. 2010;21:1560–1570. doi: 10.1681/ASN.2009111112

9. Furuland H, Linde T, Englund A, Wikstrom B. Heart rate variability is decreased in chronic kidney disease but may improve with hemoglobin normalization. *J Nephrol*. 2008;21:45–52.
10. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol*. 2008;51:1725–1733. doi: 10.1016/j.jacc.2008.01.038
11. Huang BS, Wang H, Leenen FH. Chronic central infusion of aldosterone leads to sympathetic hyperreactivity and hypertension in Dahl S but not Dahl R rats. *Am J Physiol Heart Circ Physiol*. 2005;288:H517–H524. doi: 10.1152/ajpheart.00651.2004
12. Spallone V, Gambardella S, Maiello MR, Barini A, Frontoni S, Menzinger G. Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. *Diabetes Care*. 1994;17:578–584. doi: 10.2337/diacare.17.6.578
13. Wheelock KM, Jaiswal M, Martin CL, Fufaa GD, Weil EJ, Lemley KV, Yee B, Feldman E, Brosius FC III, Knowler WC, et al. Cardiovascular autonomic neuropathy associates with nephropathy lesions in American Indians with type 2 diabetes. *J Diabetes Complications*. 2016;30:873–879. doi: 10.1016/j.jdiacomp.2016.03.008
14. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation*. 1996;94:2850–2855. doi: 10.1161/01.CIR.94.11.2850
15. Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukema JW, Middeldorp S, Rosendaal FR, Dekkers OM. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Europace*. 2013;15:742–749. doi: 10.1093/europace/eus341
16. Virtanen R, Jula A, Kuusela T, Helenius H, Voipio-Pulkki LM. Reduced heart rate variability in hypertension: associations with lifestyle factors and plasma renin activity. *J Hum Hypertens*. 2003;17:171–179. doi: 10.1038/sj.jhh.1001529
17. Grübler MR, Kienreich K, Gaksch M, Verheyen N, Hartaigh BÓ, Fahrleitner-Pammer A, März W, Schmid J, Oberreither E-M, Wetzel J, et al. Aldosterone-to-renin ratio is associated with reduced 24-hour heart rate variability and QTc prolongation in hypertensive patients. *Medicine (Baltimore)*. 2016;95:e2794. doi: 10.1097/MD.0000000000002794
18. Lu DY, Yang AC, Cheng HM, Lu TM, Yu WC, Chen CH, Sung SH. Heart rate variability is associated with exercise capacity in patients with cardiac syndrome X. *PLoS One*. 2016;11:e0144935. doi: 10.1371/journal.pone.0144935
19. Li HR, Lu TM, Cheng HM, Lu DY, Chiou CW, Chuang SY, Yang AC, Sung SH, Yu WC, Chen CH. Additive value of heart rate variability in predicting obstructive coronary artery disease beyond Framingham risk. *Circ J*. 2016;80:494–501. doi: 10.1253/circj.CJ-15-0588
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006
21. Goldberger AL, Amaral LA, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation*. 2000;101:E215–E220. doi: 10.1161/01.CIR.101.23.e215
22. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol*. 2000;278:H2039–H2049. doi: 10.1152/ajpheart.2000.278.6.H2039
23. Lu TH, Lee MC, Chou MC. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. *Int J Epidemiol*. 2000;29:336–343. doi: 10.1093/ije/29.2.336
24. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology*. 2011;22:582–585. doi: 10.1097/EDE.0b013e31821db37e
25. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274. doi: 10.7326/M16-2607
26. Stacey T, Tennant P, McCowan L, Mitchell EA, Budd J, Li M, Thompson J, Martin B, Roberts D, Heazell A. Gestational diabetes and the risk of late stillbirth: a case-control study from England, UK. *BJOG*. 2019;126:973–982.
27. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. *Nat Rev Nephrol*. 2012;8:293–300. doi: 10.1038/nrneph.2012.19
28. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, Joles JA. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol*. 2017;28:1023–1039. doi: 10.1681/ASN.2016060666
29. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. *Clin J Am Soc Nephrol*. 2015;10:382–389. doi: 10.2215/CJN.03080314
30. Fontsere N, Salinas I, Bonal J, Bayes B, Riba J, Torres F, Rios J, Sanmarti A, Romero R. Are prediction equations for glomerular filtration rate useful for the long-term monitoring of type 2 diabetic patients? *Nephrol Dial Transplant*. 2006;21:2152–2158. doi: 10.1093/ndt/gfl221
31. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, Kleefstra N, Naimark D, Roderick P, Tonelli M, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308:2349–2360. doi: 10.1001/jama.2012.16817
32. Tonelli M, Klarenbach SW, Lloyd AM, James MT, Bello AK, Manns BJ, Hemmelgarn BR. Higher estimated glomerular filtration rates may be associated with increased risk of adverse outcomes, especially with concomitant proteinuria. *Kidney Int*. 2011;80:1306–1314. doi: 10.1038/ki.2011.280
33. DiBona GF. Physiology in perspective: the Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol*. 2005;289:R633–R641.
34. Schmieder RE, Veelken R, Schobel H, Dominiak P, Mann JF, Luft FC. Glomerular hyperfiltration during sympathetic nervous system activation in early essential hypertension. *J Am Soc Nephrol*. 1997;8:893–900. doi: 10.1681/ASN.V86893
35. Sochett EB, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *J Am Soc Nephrol*. 2006;17:1703–1709. doi: 10.1681/ASN.2005080872
36. Luippold G, Beilharz M, Muhlbauer B. Chronic renal denervation prevents glomerular hyperfiltration in diabetic rats. *Nephrol Dial Transplant*. 2004;19:342–347. doi: 10.1093/ndt/gfg584
37. Hoogerwaard AF, de Jong MR, Adiyaman A, Smit JJJ, Delnoy PPHM, Heeg J-E, van Hasselt BAAM, Ramdat Misier AR, Rienstra M, van Gelder IC, et al. Renal sympathetic denervation induces changes in heart rate variability and is associated with a lower sympathetic tone. *Clin Res Cardiol*. 2019;108:22–30. doi: 10.1007/s00392-018-1307-2
38. Thio CHL, van Roon AM, Lefrandt JD, Gansevoort RT, Snieder H. Heart rate variability and its relation to chronic kidney disease: results from the PREVEND Study. *Psychosom Med*. 2018;80:307–316. doi: 10.1097/PSY.0000000000000556
39. Salman IM. Cardiovascular autonomic dysfunction in chronic kidney disease: a comprehensive review. *Curr Hypertens Rep*. 2015;17:59. doi: 10.1007/s11906-015-0571-z
40. Visser M, Kritchevsky SB, Newman AB, Goodpaster BH, Tylavsky FA, Nevitt MC, Harris TB. Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. *Am J Clin Nutr*. 2005;82:531–537. doi: 10.1093/ajcn/82.3.531