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수면호흡장애/수면무호흡증과 신장 기능의 변화 및 사망률의 관계 연구: 수면클리닉 코호트 연구

Association of Sleep-Disordered Breathing/Sleep apnea With Renal Outcome and All-Cause Mortality: A Sleep Clinic Cohort Study

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의학과 내과학 전공

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Abstract

Association of Sleep-Disordered Breathing/Sleep apnea With Renal Outcome and All-Cause Mortality: A Sleep Clinic Cohort Study

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Background: The prevalence of sleep-disordered breathing (SDB)/sleep apnea (SA) is high. SDB/SA and chronic kidney disease (CKD) share common risk factors, pathophysiological mechanisms, and are commonly comorbid with diabetes mellitus (DM), hypertension (HTN), and body mass index (BMI) in the overweight/obese range ($\geq$ 23 kg/m^2). Previous research has mostly focused on the correlations between SDB/SA and renal function. The present study investigated the effects of SDB/SA on renal function decline in patients with DM, HTN, CKD, and in overweight/obese individuals. The rapid decline of the estimated glomerular filtration rate (eGFR; RDeG) has been reported to be a risk factor for all-cause mortality (ACM); therefore, the impact of SDB/SA on ACM was also investigated.

Methods: We conducted a longitudinal analysis of a sleep clinic cohort. In analysis I, we enrolled and followed all adult subjects who were referred for diagnostic testing for SDB/SA between March 2007 and July 2014, had undergone polysomnography, and whose test records for serum creatinine levels were available. In analysis

II, Patients with predominate central sleep apnea (CSA) are commonly comorbid with heart disease or cerebrovascular disease and may have higher rates of mortality, therefore, they were excluded from the analysis I cohort. The measured outcomes of both analyses were ACM and RDeG.

Results: A total of 1,454 participants were included in analysis I. Of these, 103 patients (7.08%) had CKD and 38 patients (2.61%) died during the study. CKD was associated with severe SDB [odds ratio (OR) = 1.74 (1.12−2.70), $p < 0.05$]. CSA was associated with RDeG in the cohort [adjusted hazard ratio (HR) = 2.451 (1.193−5.037), p = 0.015], DM subjects [adjusted HR = 2.951 (1.032−8.434), p = 0.043], HTN subjects [adjusted HR = 2.524 (1.146−5.558), p = 0.022] and overweight/obese subjects [adjusted HR = 3.207 (1.528−6.73), p = 0.002]. Obstructive sleep apnea (OSA) was a risk factor for RDeG in CKD patients [adjusted HR = 3.242 (1.235−8.51), p = 0.017]. CSA was a risk factor for ACM in the cohort [adjusted HR = 4.642 (1.749−12.322), p = 0.002], DM [adjusted HR = 10.285 (2.285−46.281), p = 0.002], HTN [adjusted HR = 5.797 (1.558−21.574), p = 0.009], CKD [adjusted HR = 11.093 (2.671−46.069), p = 0.001], and overweight/obese subjects [adjusted HR = 7.317 (2.535−21.124), $p < 0.001$]. In analysis II, the respiratory disturbance index (RDI) was found to be a risk factor for RDeG in the cohort [adjusted HR = 1.007 (1−1.015), p = 0.047], CKD subjects [adjusted HR = 1.038 (1.001−1.075), p = 0.043], and overweight/obese subjects [adjusted HR= 1.011 (1.004−1.019), p = 0.005]. The obstructive apnea index (AI)−to−respiratory disturbance index (RDI) ratio predicted the risk of death in the cohort [adjusted HR = 1.015 (1.002−1.028), p = 0.033], DM subjects [adjusted HR = 1.053 (1.01−1.099), p = 0.016], and HTN subjects [adjusted HR = 1.036 (1.008−1.064), p = 0.01], whereas RDI was a risk factor for ACM in CKD subjects [adjusted HR = 1.063 (1.005−1.123), p = 0.032].

Conclusion: In the present study, CKD was associated with severe SDB (RDI ≥ 30/h). SDB/SA was a predictor/risk factor for the rapid decline of eGFR in the cohort and in patients with CKD or who

were overweight/obese. SDB/SA also predicted the risk of death in the cohort and in patients with HTN/DM/CKD. A multi-step approach that uses a variety of therapeutic modalities is recommended for SDB/SA in DM/HTN/CKD patients to reduce the mortality risk.

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Keywords: sleep apnea; chronic kidney disease; all-cause mortality; sleep disordered breathing; renal function decline

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Contents

List of tables

List of figures

List of abbreviations

ACE, Angiotensin converting enzyme
ARB, Angiotensin receptor blocker
OHA, Oral hypoglycemic agents.
CKD, Chronic kidney disease
CVD, cerebrovascular disease
CHD, coronary heart disease
HTN, Hypertension
DM, Diabetes mellitus
BMI, Body mass index.
NSAID, Non-steroidal anti-inflammatory drugs
SDB, Sleep disordered breathing
SA, Sleep apnea
CSA, Central sleep apnea
MSA, Mixed sleep apnea
OSA, Obstructive sleep apnea
NH, Nocturnal hypoxia
REM, Rapid eye movement sleep
HI, Hypopnea index
AI, Apnea index
RDI, Respiratory disturbance index
RDI groups, Respiratory disturbance index ≥5/h, 15/h, and 30/h
TST, Total sleep time
SWS, Slow-wave sleep.
RDeG, Rapid decline of eGFR
ACM, All-cause mortality
CVM, Cardiovascular mortality
HR, Hazard ratio
CI, confidence interval

Chapter 1. Introduction

Sleep-disordered breathing (SDB) usually represents a set of disorders of abnormal respiratory patterns or insufficient ventilation and is associated with intermittent hypoxemia and arousals during sleep (1). SDB primarily manifests as one of three types of sleep apnea (SA): obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed sleep apnea (MSA). The estimated prevalence of SDB has increased over the last 2 decades (relative increases of between 14-55%) in adults. A current population-based study has reported that the prevalence of mild-to-severe SDB (apnea-hypopnea index (AHI) ≥ 5 events/h) is 83.8% in men and 60.8% in women, whereas the prevalence of moderate-to-severe SDB (AHI ≥ 15 events/h) is estimated to be 49.7% in men and 23.4% in women (2)

Chronic kidney disease (CKD), defined as either kidney damage or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, severely affects a patient's health, work, and well-being. Diabetes mellitus (DM) and hypertension (HTN) are significant contributors to the increased prevalence of CKD (3). The estimated prevalence of CKD is between 8% and 16% worldwide (4). In Asian countries, approximately 13% of the population in Japan is afflicted with CKD, most with stage 3 (eGFR < 60 mL/min/1.73 m^2, 2002, KQOQI) of the disease. Nearly 11% of the population in China is afflicted with CKD, most of whom have either at stage 1 or 2 CKD (5). The prevalence of CKD in urban Korea was estimated to be 13.7% in 2009, with 5% of the population afflicted with stage 3 CKD (6). Considering that the population is aging, the expenditure on CKD management is increasing globally.

SDB/SA and CKD share common risk factors such as sex, older age, and overweight/obese body mass index (BMI) (7, 8). SDB/SA is more common in patients with CKD (41%) (9) and is especially

high in patients on dialysis (> 50%) (10, 11) compared to the general population (20%) (12). The pathophysiological link between SDB/SA and CKD may be through neurohumoral changes, oxidative stress, inflammation, endothelial dysfunction, and/or fibrinolysis imbalance (13-16). Recent findings have documented a considerable increase in the incidence of CKD in SDB/SA patients. The prevalence of CKD in the sleep disordered breathing population is 3 times higher than in the non-SDB group (30.5% vs. 9.1%), with an adjusted odds ratio of 4.542 (17).

Most of the previous studies were cross-sectional, and were centered on correlations between SDB/SA and renal function (18-20). Studies on the effects of SDB/SA on renal function are scarce. Though a few prospective cohort studies investigating the effect of SDB/SA on outcomes that concentrated on dialyzed CKD or renal transplant patients (21, 22), data on the contributions of SDB/SA to renal outcome in the non-dialyzed CKD population are insufficient. SDB/SA and CKD are commonly comorbid with DM, HTN, and overweight/obesity (23-25). SDB was correlated with renal impairment in patients with DM (26). Severe SA, stage III HTN, and resistant HTN are independent risk factors for CKD, and patients with both severe SA and HTN have the highest risk for CKD (25). In obese adults (BMI 48.3 ± 8.9 kg/m^2), the severity of OSA was found to be associated with higher serum creatinine (24). The data regarding the effects of SDB/SA on renal outcome in DM, HTN, or overweight/obesity subjects are also insufficient. Therefore, the impact of SDB/SA on renal outcomes in subjects with DM/HTN/CKD and those who are overweight/obese was investigated in our study.

Providing that there is a pathophysiological link between SDB/SA and CKD, SDB/SA may have potentially detrimental effects on renal function. The rapid decline of eGFR (RDeG) is associated with all-cause mortality (ACM) in older adults (27). SDB/SA may rapidly worsen renal function and increase ACM. To better characterize the effect of SDB/SA on ACM in non-dialyzed CKD

subjects and also in those with DM, HTN, or those who are overweight/obese, further investigation is necessary.

Chapter 2. Methods

2.1 Data source

For analysis I, we enrolled non-dialyzed patients (age ≥ 18 years) who had not undergone kidney transplantation, who had undergone polysomnography (PSG), and whose records for serum creatinine levels had been measured within 3 months of the PSG examination **(Fig. 1)**. These patients were treated at the Seoul National University, Bundang Hospital (SNUBH) between March 2007 and July 2014. The Institutional Review Board of the Seoul National University Bundang Hospital (SNUBH) (IRB No. B-1412/278-123) approved this study. None of the patients belonged to a vulnerable population or were subjected to coercion. Skilled respiratory experts performed SDB impression tests. The date of participant enrollment was defined as the date of the first SA diagnosis. End-stage renal disease (ESRD) patients undergoing dialysis were identified from the ESRD registry in Korea and excluded. Patients who underwent kidney transplantation or who were transferred to hemodialysis or peritoneal dialysis were censored at the time of transfer to alternative renal replacement therapy. For analysis II, since patients with predominate CSA are commonly comorbid with heart disease or cerebrovascular disease and may have higher rates of mortality, we excluded patients with predominate CSA from the cohort of analysis I. Baseline information, including age, sex, BMI, neck circumference, and obesity status was obtained for all participants at the time of sleep diagnostic testing. Data on variables such as major comorbidities, including DM, hypertension, dyslipidemia, coronary artery disease (CHD), cerebrovascular disease (CVD), and cancer were collected.

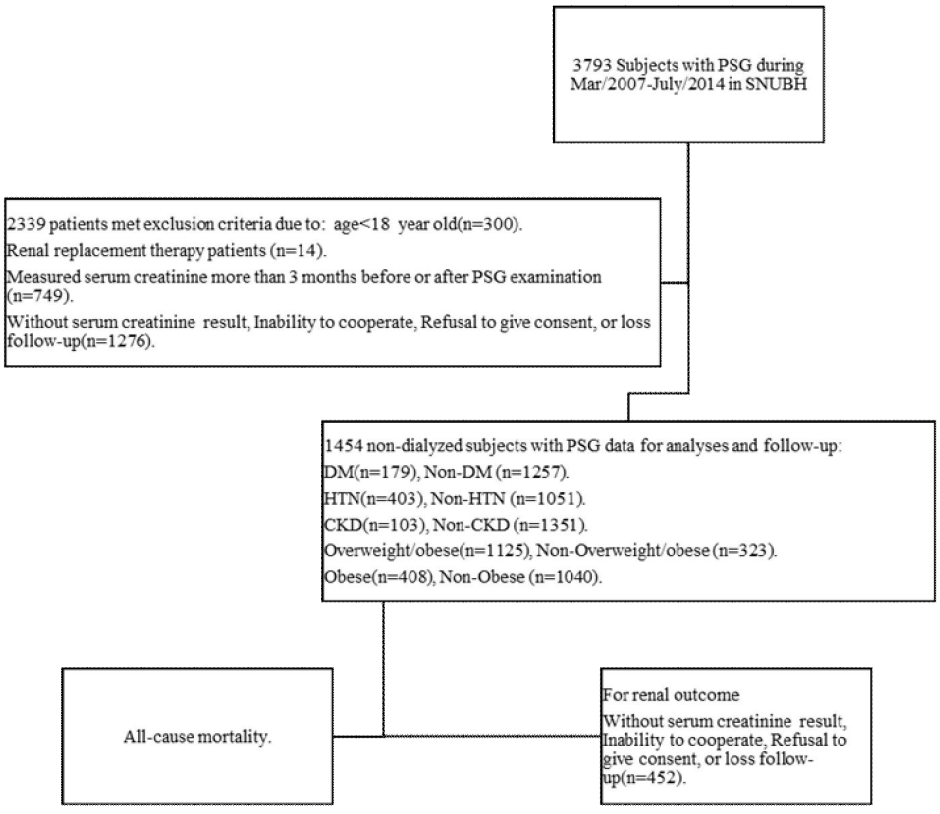
3793 Subjects with PSG during Mar/2007-July/2014 in SNUBH
2339 patients met exclusion criteria due to: age<18 year old(n=300).
Renal replacement therapy patients (n=14).
Measured serum creatinine more than 3 months before or after PSG examination (n=749).
Without serum creatinine result, Inability to cooperate, Refusal to give consent, or loss follow-up(n=1276).
1454 non-dialyzed subjects with PSG data for analyses and follow-up:
DM(n=179), Non-DM (n=1257).
HTN(n=403), Non-HTN (n=1051).
CKD(n=103), Non-CKD (n=1351).
Overweight/obese(n=1125), Non-Overweight/obese (n=323).
Obese(n=408), Non-Obese (n=1040).
All-cause mortality.
For renal outcome
Without serum creatinine result, Inability to cooperate, Refusal to give consent, or loss follow-up(n=452).

Fig.1 Flow diagram of patient recruitment process. PSG, Polysomnography; SNUBH, Seoul National University Bundang hospital ; CKD, Chronic kidney disease; DM, diabetes mellitus; HTN, hypertension.

Information on concomitant medication use associated with the physical condition during the first 30 days of enrollment was also extracted. Medications were categorized as anti-platelet agents, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocker inhibitors, anti-hypertension drugs, anti-lipid drugs, anti-platelet drugs, anti-hyperglycemic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and diuretics. Some blood and urine test results were available.

Patients were subjected to a standardized questionnaire. Diabetes was defined as fasting plasma glucose concentration ≥ 7.0 mmol/L and/or current drug treatment for diabetes. Hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or current drug treatment for hypertension (28). The World Health Organization Asian criteria were used to define the overweight/obese BMI range (BMI ≥ 23 kg/m^2) (29).

2.2 Polysomnography

Polysomnography was performed using an Embla N7000 (Embla, Reykjavik, Iceland) equipped with standard electrodes and sensors. Electroencephalography electrodes were applied at C4/A1, C3/A2, O1/A2, and O2/A1, and two electrooculography electrodes were applied on the sides of both eyes to record horizontal and vertical eye movements. Electromyography electrodes were applied on the submentalis muscles and both anterior tibialis muscles. Strain gauges were used for recording chest and abdominal respiratory movements, and nasal pressure cannulae were used to record airflow. Oxygen saturation was measured using a pulse oximeter

applied to the index finger. Sleep patterns were scored in 30-s epochs of the nocturnal polysomnography. An independent sleep medicine expert scored all polysomnograms manually using standard criteria (30-32).

Apnea was defined as the cessation of airflow for 10 s, and hypopnea was defined as a reduction of airflow by ≥ 50% for 10 s with an oxygen desaturation < 4%. The average number of episodes of apnea and hypopnea per hour of sleep (apnea-hypopnea index, AHI) was determined as the summary measurement of SDB. The respiratory disturbance index (RDI) is another index for evaluating the presence and severity of sleep apnea (30). The RDI is the sum of the apnea-hypopnea index (AHI) and the respiratory effort-related arousal (RERA) index. Subjects with an RDI of 5 to 14.9, 15 to 29.9, and 30 or higher were considered to have mild, moderate, and severe SDB, respectively (33).

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Desaturation index (DI) was defined as the mean number of episodes of SaO_2 decrease ≥ 4% per hour of sleep. Hypopnea index (HI) was defined as a reduction in airflow ≥ 30% for at least 10 s with a desaturation of ≥ 3% or with respiratory arousal from sleep.

Sleep apnea was arbitrarily defined as an AHI ≥ 5 events per hour of sleep (34). Apnea was classified as central (CSA) if there was no chest and abdominal movement, obstructive (OSA) if it was caused by complete or partial obstruction of the upper airway, and mixed (MSA) if an initial absence of ventilatory effort was followed by an obstructive apnea pattern on resumption of effort. Clinically, MSA has been considered as a variant of OSA, but not CSA (35); therefore, we considered MSA events as OSA events (OSA extend). Nocturnal hypoxia (NH) was defined as an SaO_2 below 90% for ≥ 12% of the total nocturnal monitoring time.

2.3 Main outcome

The CKD was defined based on an eGFR < 60 mL/min/1.73 m^2. eGFR was calculated using the GFR-CKD-EPI equation with IDMS-traceable creatinine. The outcomes evaluated were all-cause mortality (ACM) and renal outcome. Mortality was identified from the National Registry data. Renal outcome was measured by RDeG, an eGFR decrease ≥ 25%, and a change in the GFR stage or a GFR decline ≥ 5 mL/min/1.73 m^2/year by the KDIGO guidelines, as previously reported by Katalin Fornadi et al. (36). All subjects were followed from the index date until death, withdrawal, or July 2014.

2.4 Statistical analysis

All data are expressed as mean ± standard deviation or percentages unless otherwise stated. Data from the two groups were compared using independent Student's t-tests or Mann-Whitney U tests for continuous variables, and chi-square tests for categorical variables, as appropriate. Initially, statistical significance was inferred when two-sided P values were < 0.05. However, Bonferroni correction was also considered to control type 1 error. Multivariate linear regression was used to analyze the relationship between the RDI and renal function parameters while adjusting for confounding variables such as age, BMI, sex, DM, and HTN. Prior to the multivariate linear regression, the variables were evaluated for the assumptions of linear regression. The dependent variable was not normally distributed and was subsequently transformed to a ranked normal score using Blom's formula (37). Spearman's rank correlation was used to decide which variables to put into the multivariate regression. All variables with significant correlations (i.e., $p < 0.05$) with the dependent variable in Spearman's rank correlation were put into the final multivariate linear regression. Survival analysis was performed using the Kaplan-Meier method,

with significance based on the log-rank test. A logistic regression model was employed to evaluate the correlations between CKD and the severity of SDB. Odds ratios (OR) were adjusted for all potential risk factors of SDB/SA such as age, sex, neck circumference, DM, and HTN. For evaluation of the effect of SDB/SA on ACM and renal outcome, factors predictive of mortality and renal outcome were identified using univariate analysis and then introduced into a Cox proportional hazard model to deduce the hazard ratios and 95% confidence intervals. Factors with $p < 0.25$ on univariate analysis were entered into a multivariable Cox regression model. A forward elimination procedure with $p > 0.05$ was performed to identify independent predictors of ACM and renal outcome. Goodness of fit was checked in regression model selection to control for over-fitting. All statistical analyses were performed using SPSS (IBM SPSS statistics version 21.0, IBM Corporation, Armonk, NY).

Chapter 3. Results.

3.1 Baseline characteristics and PSG results

During the study period, 3,793 participants with PSG results were referred to the study. As outlined in **Fig. 1**, 2,339 participants (61.6%) did not meet the inclusion criteria, resulting in a final study cohort of 1,454 subjects (38.4%). The cohort included 1,058 males (72.8%) and had a mean age of 53.7 ± 13.8 years and a mean BMI of 25.7 ± 3.8 kg/m^2. Within the cohort, 179 patients (12.3%) had DM, 403 (27.7%) had HTN, 103 (7.08%) had CKD, and 1,125 (77.4%) were overweight/obese. A total of 1,171 patients (80.5%) had mild SDB (RDI ≥ 5/h), 820 (56.4%) had moderate SDB (RDI ≥ 15/h), and 487 (33.5%) had severe SDB (RDI ≥ 30/h). Moreover, 105 patients (7.2%) had MSA, 724 (49.8%) had OSA, 729 (50.1%) had OSA extend, and 33 (2.3%) had CSA. One hundred and ninety-seven patients (13.5%) had NH **(Table 1).**

Table 1. Baseline parameters of the cohort

Physical parameters	
Male (%)	72.8%
Age (years)	53.72±13.80
BMI (kg/m^2)	25.69±3.76
Waist to Hip ratio (%)	1.10±3.58
Neck circumference (cm)	37.74±11.21
Hip circumference (cm)	98.96±7.50
Waist circumference (cm)	92.68±26.06
Comorbidities:	
Prevalence of diabetes N (%)	12.3
Prevalence of hypertension N (%)	27.7
Prevalence of coronary heart	4.8

disease N (%)	
Prevalence of cerebrovascular disease N (%)	4.9
Prevalence of cancer N (%)	8.6
Prevalence of CKD N (%)	7.1
Laboratory parameters	
eGFR at baseline ml/min./1.73 m^2)	87.88±18.68
Blood Hemoglobin (g/dL)	14.42±1.74
Serum albumin (g/dL)	4.41±0.37
Serum cholesterol (mg/dL)	185.47±36.59
Medications:	
ACE inhibitors or ARBs N (%)	13.3
Anti-hypertensive drug N (%)	22.4
Anti-NSAID drug N (%)	12
Anti-Lipid drugs N (%)	13.8
Anti-platelet drugs N (%)	16.1
Diuretics N (%)	4.9
Insulin drugs N (%)	3.2
OHA drugs N (%)	7.9
Sleep architectures:	
Sleep efficiency (% TST)	79.90±13.47
Stage 1 (% TST)	13.68±9.25
Stage 2 (% TST)	49.88±13.05
Stage 3 (% TST)	5.31±6.46
Stage 4 (% TST)	0.23±1.59
SWS (% TST)	5.54±6.82
REM (% TST)	14.88±7.61
Respiratory arousal (/h)	18.36±19.80
Sleep parameters	
RDI(/h)	25.14±22.95
Apnea index AI (/h)	14.10±19.53
Central AI (/h)	0.49±2.05
Obstructive AI (/h)	12.22±17.43
Mixed AI (/h)	1.41±5.16

Hypopnea index (/h)	11.08±10.37
Desaturation index (/h)	19.66±21.39
SaO_2 <90% (/h)	5.75±13.043
RDI≥5/h N (%)	80.50
RDI≥15/h N (%)	56.4
RDI≥30/h N (%)	33.5
Nocturnal hypoxia N (%)	13.5
MSA N (%)	7.2
OSA N (%)	49.8
OSA extend N (%)	50.1
CSA N (%)	2.3
HI≥5/h N (%)	66.5
AI≥5/h N (%)	52

Abbreviations: ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blocker; CKD, Chronic kidney disease; NSAID, Non-steroidal anti-inflammatory drugs. CSA, Central sleep apnea(Central AI<5/h); MSA, Mixed sleep apnea; OSA, obstructive sleep apnea; REM, Rapid eye movement sleep; HI, Hypopnea index; AI, Apnea index; RDI, Respiratory disturbance index; TST, Total sleep time; SWS, Slow-wave sleep.

Subjects with CKD tended to be older males, and were also more likely to have comorbidities such as HTN, DM, cancer, and other diseases. CKD subjects were also more likely to take anti-HTN, anti-lipid, anti-platelet, and diuretic drugs than non-CKD subjects. Patients with CKD had lower sleep efficiency, and less stage 2, stage 3 time, slow-wave sleep (SWS), and rapid eye movement (REM) sleep than non-CKD patients. The central AI and the hypopnea index (HI) of CKD patients were higher than in non-CKD subjects. OSA was the most common type of SA in our cohort, but statistical differences between CKD and non-CKD patients were only found in patients with CSA or MSA. There were more patients with SDB (RDI ≥ 30/h and RDI ≥15/h) in the CKD group than in

the non-CKD group, while no such trends were found in patients with SDB (RDI ≥ 5/h). CKD patients seemed more likely to experience NH; however, there was no significant difference in comparison to the non-CKD group (Table 2).

Table 2. Baseline parameters of patients with and without chronic kidney disease.

	non-CKD	CKD	P-value
Numbers	1351	103	
Male (%)	73.9	58.3	*0.001*
Age (years)	52.6 ± 13.3	68.6 ± 11.1	*<0.001*
BMI (kg/m2)	25.7 ± 3.8	25.7±3.4	0.939
Obese (BMI>28kg/m2) N (%)	24.2	23.2	0.6
Waist to Hip ratio (%)	1.10 ± 3.71	1.02 ± 0.79	0.817
Neck circumference(cm)	37.8 ± 11.6	37.1 ± 3.3	0.572
Comorbidities			
Prevalence of diabetes N (%)	11.5	22.3	*0.003*
Prevalence of hypertension N (%)	25.8	53.4	*<0.001*
Prevalence of coronary heart disease N (%)	4.5	8.7	0.088
Prevalence of cerebrovascular disease N (%)	4.3	12.6	*0.001*
Prevalence of cancer N (%)	8.1	14.6	*0.042*
Laboratory parameters			
eGFR at baseline ml/min./1.73 m^2)	90.8 ± 15.6	48.9 ± 11.1	*<0.001*
Blood Hemoglobin	14.48±0.049	13.58±0.19	*<0.001*

(g/dL)			
Serum albumin (g/dL)	4.42±0.01	4.27±0.04	*<0.001*
Serum cholesteral (mg/dL)	186.22±1.01	175.39±4.01	*0.01*
Medications			
ACE inhibitors or ARBs N (%)	12.1	30.1	*<0.001*
Anti-hypertensive drug N (%)	20.7	44.7	*<0.001*
Anti-NSAID drug N (%)	11.8	14.6	0.4
Anti-Lipid drugs N (%)	12.8	26.2	*<0.001*
Anti-platelet drugs N (%)	14.8	33	*<0.001*
Diuretics N (%)	3.8	18.4	*<0.001*
Sleep architectures			
Sleep efficiency (% TST)	80.5 ± 13.0	71.6 ± 16.4	*<0.001*
Stage 1 (% TST)	13.6 ± 9.2	14.1 ± 9.5	0.624
Stage 2 (% TST)	50.1 ± 13.0	46.7 ± 13.7	*0.011*
Stage 3 (% TST)	5.47± 0.18	3.11± 0.5	*<0.001*
Stage 4 (% TST)	0.25± 0.045	0.08± 0.006	0.142
SWS (% TST)	5.7 ± 6.9	3.1 ± 5.0	*<0.001*
REM (% TST)	15.0 ± 7.4	13.1 ± 9.3	*0.014*
Respiratory arousal (/h)	18.1 ± 20.0	20.9 ± 18.8	0.171
Sleep parameters			
Apnea index AI (/h)	14.0 ± 19.6	15.0 ± 18.2	0.645
Central AI (/h)	0.4 ± 2.0	1.0 ± 2.9	*0.008*
Obstructive AI (/h)	12.3 ± 17.7	11.4 ± 14.3	0.68
Mixed AI (/h)	1.4 ± 5.3	2.5 ± 7.2	0.116
Hypopnea index (/h)	10.8 ± 10.3	14.2 ± 11.3	*0.004*
Desaturation index (/h)	19.4 ± 21.5	23.1 ± 19.9	0.091
SaO_2 <90% (/h)	5.7 ± 13.1	6.8 ± 12.3	0.471
RDI≥5/h N (%)	80.2	85.4	0.193

RDI≥15/h N (%)	55.5	68	*0.019*
RDI≥30/h N (%)	32.6	45.6	*0.009*
Nocturnal hypoxia N (%)	13.2	17.5	0.29
MSA N (%)	6.8	12.6	*0.046*
OSA N (%)	49.5	53.4	0.448
OSA extend N (%)	49.7	55.3	0.267
CSA N (%)	1.9	6.8	*0.004*
HI≥5/h N (%)	65.8	75.7	*0.05*
AI≥5/h N (%)	51.4	59.2	0.128

Abbreviations: ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blocker; CKD, Chronic kidney disease; NSAID, Non-steroidal anti-inflammatory drugs. CSA, Central sleep apnea(Central AI<5/h); MSA, Mixed sleep apnea; OSA, obstructive sleep apnea; REM, Rapid eye movement sleep; HI, Hypopnea index; AI, Apnea index; RDI, Respiratory disturbance index; TST, Total sleep time; SWS, Slow-wave sleep.

SDB (RDI ≥ 30/h, RDI ≥ 15/h, and RDI ≥ 5/h), NH, CSA, OSA, and OSA extend were more common in DM versus non-DM subjects, whereas SDB (RDI ≥ 30/h, RDI ≥ 15/h, and RDI ≥ 5/h), CSA, MSA, OSA and OSA extend were more common in HTN versus non-HTN subjects. Compared with non-overweight/obese subjects, overweight/obese subjects more commonly had SDB (RDI ≥ 30/h, RDI ≥ 15/h, and RDI ≥ 5/h), MSA, OSA, and OSA extend (Table 3).

Table 3. Sleep disordered breathing /sleep apnea in patients with and without diabetes mellitus, hypertension, overweight/obese.

	Diabetes	Non-Diabetes	P-value
Number	179	1275	
RDI≥5/h N (%)	88.8	79.4	*0.003*

RDI≥15/h N (%)	71.7	54.3	*<0.001*
RDI≥30/h N (%)	46.4	31.7	*<0.001*
MSA N (%)	10.6	6.7	0.061
OSA N (%)	60.3	48.3	*0.003*
OSA extend N (%)	61.5	48.5	*0.001*
CSA N (%)	4.5	2	*0.035*
	HTN	Non-HTN	P-value
Number	403	1051	
RDI≥5/h N (%)	88.8	77.4	*<0.001*
RDI≥15/h N (%)	68	52	*<0.001*
RDI≥30/h N (%)	44.4	29.3	*<0.001*
CSA N (%)	4	1.6	*0.007*
MSA N (%)	10.9	5.8	*0.001*
OSA N (%)	58	46.3	*<0.001*
OSA extend N (%)	59.6	46.4	*<0.001*
	Overweight /obese	Non-Overweight /obese	P-value
Number	1125	323	
RDI≥5/h N (%)	86.1	61	*<0.001*
RDI≥15/h N (%)	62.6	34.7	*<0.001*
RDI≥30/h N (%)	38.1	17	*<0.001*
CSA N (%)	2.5	1.5	0.318
MSA N (%)	8.1	3.7	*0.007*
OSA N (%)	54.6	32.8	*<0.001*
OSA extend N (%)	54.9	32.8	*<0.001*

Abbreviations: CSA, Central sleep apnea (Central AI<5/h); MSA, Mixed sleep apnea; OSA, obstructive sleep apnea; RDI, Respiratory disturbance index.

3.2 SDB and renal function

RDI was significantly correlated with BMI ($r = 0.395$, $p < 0.001$), sex ($r = 0.265$, $p < 0.001$), DM ($r = 0.139$, $p < 0.001$), HTN ($r =$

0.186, p < 0.001), blood urea nitrogen (BUN) (r = 0.094, p < 0.001), and eGFR (r = − 0.054, p = 0.04). However, in the multivariate linear regression analysis, lower eGFR was not associated with higher transformed RDI, whereas higher BUN was associated with higher transformed RDI (p = 0.015) in the adjusted model. (Table 4).

Table 4. Correlations between RDI and renal function parameters

	Spearman Rank Correlation		Multivariate linear regression	
	r	p−value	β	p−value
Blood urea nitrogen	0.094	*<0.001*	0.011	*0.015*
eGFR	−0.054	*0.04*		
Sex	0.265	*<0.001*	0.518	*<0.001*
Age	0.049	0.062		
BMI	0.395	*<0.001*	0.099	*<0.001*
Diabetes mellitus	0.139	*<0.001*	0.248	*0.001*
Hypertension	0.186	*<0.001*	0.268	*<0.001*

Our study investigated the correlation between CKD and the severity of SDB. In the univariate analysis, after Bonferroni correction, there was a statistical difference in subjects with an RDI ≥ 30/h (severe SDB) between the CKD and non−CKD groups. The results of the logistic regression analysis of the CKD patients are provided in Table 5. The prevalence of severe SDB (RDI ≥ 30/h) in our cohort was 1.738 times higher among patients with versus without CKD in the unadjusted model. This number decreased to 1.732 times after the data were adjusted for age and sex, and to 1.737 times after the data were adjusted for age, sex, neck circumference, DM, and HTN.

Table 5. Association between chronic kidney disease and severe sleep disordered breathing (RDI ≥ 30/h)

	Unadjusted Model	Multivariate adjusted model1	Multivariate adjusted model2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
CKD and severe SDB (RDI≥30/h)			
CKD (vs non-CKD)	1.738 (1.160-2.603)	1.732 (1.113-1.119)	1.737 (1.119-2.695)

Model1 was adjusted for age, gender, obese.
Model2 was adjusted for age, gender, obese, neck circumference, DM, and HTN

Abbreviations: OR, Odds ratio; HTN, Hypertension; DM, Diabetes mellitus; CKD, Chronic Kidney Disease; SDB, sleep disordered breathing; RDI, Respiratory disturbance index.

Over a follow-up period of 30.7 ± 25.1 (mean ± SD) months, 150 (15.0%) of the 1,002 participants were identified as having RDeG. RDI predicted RDeG [adjusted HR = 1.011 (1.004-1.017), p = 0.002; Cox hazard model] after adjusting RDI for categorical and continuous values. RDI remained a risk factor for RDeG in the fully adjusted model [adjusted HR = 1.008 (1.001-1.015), p = 0.026; Cox hazard model] (Table 6). The rapid loss of kidney function was greater in subjects with CSA, MSA, or NH compared to participants without CSA (p = 0.003), MSA (p < 0.001), or NH (p = 0.002) in the univariate analysis. When MSA was included in OSA extend, CSA was a risk factor for RDeG [adjusted HR = 2.451 (1.193-5.037), p = 0.015], DM subjects [adjusted HR = 2.951 (1.032-8.434), p = 0.043], HTN subjects [adjusted HR = 2.524 (1.146-5.558), p = 0.022], and overweight/obese subjects [adjusted HR = 3.207 (1.528-6.73), p = 0.002]. OSA extend was a risk factor for

RDeG in CKD patients [adjusted HR = 3.242 (1.235−8.51), p = 0.017] (Table 7a).

Table 6. Association between sleep disordered breathing and rapid decline of eGFR

	Unadjusted Model HR (95% CI)	Multivariate adjusted model1 HR (95% CI)	Multivariate adjusted model2 HR(95% CI)	Multivariate adjusted model3 HR(95% CI)
RDI (+1event/h)	1.011 (1.004−1.017)	1.011 (1.004−1.017)	1.011 (1.004−1.017)	1.008 (1.001−1.015)

Model 1 was adjusted for age, sex, BMI, RDI and RDI groups.

Model 2 was adjusted for age, sex, BMI, RDI and RDI groups, DM, and HTN.

Model 3 was adjusted for age, sex, BMI, RDI and RDI groups, DM, HTN, anti−HTN drugs, insulin, bilirubin, alkaline phosphatase, cholesterol, platelet, and hemoglobin.

Abbreviations : RDI, Respiratory disturbance index; HR, Hazard ratio; CI, confidence interval; HTN, hypertension; DM, Diabetes mellitus; BMI, Body mass index. DM, diabetes mellitus; HR, hazard ratio; HTN, RDI groups, respiratory disturbance index ≥5/h, 15/h, and 30/h.

Table 7a. Association between sleep disordered breathing/sleep apnea and rapid decline of eGFR

Association between SA and rapid decline of eGFR in the cohort				
	Unadjusted Model HR (95% CI)	Multivariate adjusted model1 HR (95% CI)	Multivariate adjusted model2 HR (95% CI)	Multivariate adjusted model3 HR (95% CI)

CSA (vs non-CSA)	2.825 (1.385-5.761)	2.652 (1.296-5.426)	2.366 (1.153-4.856)	2.451 (1.193-5.037)
Model 1 was adjusted for older age, sex, obesity, CSA, OSA extend, NH, and RDI groups. Model 2 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, DM, and HTN. Model 3 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, DM, HTN, anti-HTN drugs, OHA, bilirubin and cholesterol.				
DM subjects.				
CSA (vs non-CSA)	2.789 (0.978-7.953)	2.797 (0.979-7.991)	3.006 (1.051-8.592)	2.951 (1.032-8.434)
Model 1 was adjusted for older age, sex, obesity, CSA, OSA extend, NH, and RDI groups. Model 2 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, and HTN. Model 3 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, HTN, anti-HTN drugs, bilirubin and cholesterol.				
HTN subjects.				
CSA (vs non-CSA)	2.9 (1.329-6.329)	2.586 (1.174-5.698)	2.586 (1.174-5.698)	2.524 (1.146-5.558)
Model 1 was adjusted for older age, sex, obesity, CSA, OSA extend, NH, and RDI groups. Model 2 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, and DM. Model 3 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, DM, OHA, bilirubin and cholesterol.				
CKD patients				
OSA extend (vs non-OSA	2.309 (1.029-5.179)	2.382 (1.011-5.613)	2.382 (1.011-5.613)	3.242 (1.235-8.51)

extend)				
Model 1 was adjusted for older age, sex, obesity, CSA, OSA extend, NH, and RDI groups. Model 2 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, HTN and DM. Model 3 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, HTN, DM, OHA, alkaline phosphatase, and hemoglobin.				
Overweight/obese subjects				
CSA (vs non-CSA)	4.203 (2.041-8.654)	3.703 (1.786-7.676)	3.342 (1.606-6.955)	3.207 (1.528-6.73)
Model 1 was adjusted for older age, sex, obesity, CSA, OSA extend, NH, and RDI groups. Model 2 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, HTN and DM. Model 3 was adjusted for older age, sex, CSA, OSA extend, NH, RDI groups, DM, HTN, anti-HTN drugs, OHA, bilirubin and cholesterol.				

Abbreviations : CSA, central sleep apnea; OSA, obstructive sleep apnea; NH, nocturnal hypoxia RDI, Respiratory disturbance index; HR, Hazard ratio; CI, confidence interval; HTN, hypertension; DM, Diabetes mellitus; BMI, Body mass index. DM, diabetes mellitus; HR, hazard ratio; HTN, RDI groups, respiratory disturbance index ≥5/h, 15/h, and 30/h.

In non-CSA subjects, RDI was a risk factor for RDeG [adjusted HR = 1.007 (1-1.015), p = 0.047], CKD subjects [adjusted HR = 1.038 (1.001-1.075), p = 0.043], and overweight/obese subjects [adjusted HR = 1.011 (1.004-1.019), p = 0.005] (Table 7b).

Table 7b. Association between sleep disordered breathing/sleep

apnea and rapid decline of eGFR in subjects without central sleep apnea

Association between SDB/SA and rapid decline of eGFR in the cohort excluded CSA subjects.		
	Unadjusted Model HR (95% CI)	Fully-adjusted model HR (95% CI)
RDI (+1event/h)	1.01 (1.003-1.017)	1.007 (1-1.015)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, age, BMI, gender, DM, HTN, anti-HTN, OHA.		
Overweight/obese subjects.		
RDI (+1event/h)	1.013 (1.005-1.021)	1.011 (1.004-1.019)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, age, BMI, gender, DM, HTN, anti-HTN, OHA.		
CKD subjects.		
RDI (+1event/h)	1.038 (1.001-1.075)	1.038 (1.001-1.075)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, age, BMI, gender, DM, HTN, anti-HTN, OHA.		

Abbreviations: CI, confidence interval; HR, hazard ratio; OSA, obstructive sleep apnea; RDI, respiratory disturbance index ;RDI groups, RDI >5/h, 15/h, and 30/h. DM, diabetes mellitus; HTN, hypertension; OHA, oral hypoglycemic agents.

3. 3 SDB and all-cause mortality

During the follow-up period of 46.8 ± 25.9 months, 38 patients died. The results from the analysis of all-cause mortality (ACM) are shown in Fig. 2 and Fig. 3. The survival incidence of subjects with CSA versus non-CSA was lower at the same follow-up duration in the Kaplan-Meier (KM) analysis, and the gap between

these groups was greater in patients with DM, HTN, and CKD. KM analysis also revealed that the CSA group had a significantly worse survival rate than the non-CSA group ($p < 0.001$) in overweight/obese subjects. When MSA was included in OSA extend in the Cox regression analysis, among the risk factors identified for SDB, only CSA played a significant role in mortality. CSA was a risk factor for ACM in the whole cohort [adjusted HR = 4.642 (1.749-12.322), p = 0.002], DM [adjusted HR = 10.285 (2.285-46.281), p = 0.002], HTN [adjusted HR = 5.797 (1.558-21.574), p = 0.009], CKD [adjusted HR = 11.093 (2.671-46.069), p = 0.001], and overweight/obese patients [adjusted HR = 7.317 (2.535-21.124), p < 0.001] (Table 8a).

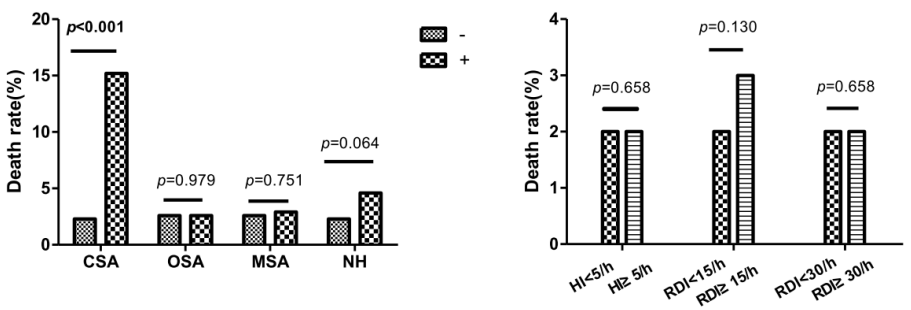

Fig.2. Death rate and sleep apnea components. Abbreviations : CSA, Central sleep apnea(Central AI<5/h); MSA, Mixed sleep apnea; OSA obstructive sleep apnea; HI, Hypopnea index; RDI, Respiratory disturbance index; NH, Nocturnal hypoxia.

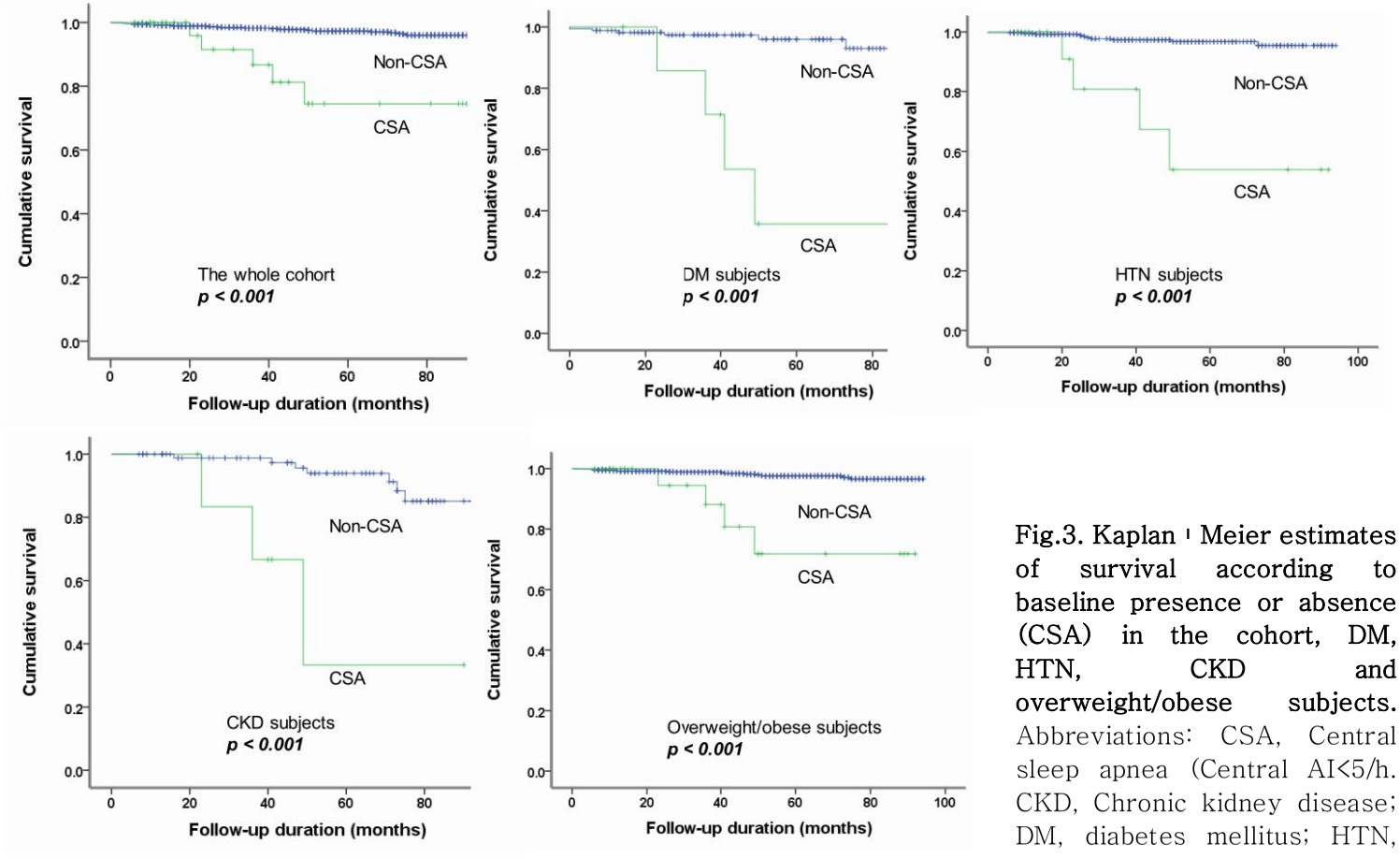

Fig.3. Kaplan ㅣ Meier estimates of survival according to baseline presence or absence (CSA) in the cohort, DM, HTN, CKD and overweight/obese subjects. Abbreviations: CSA, Central sleep apnea (Central AI<5/h. CKD, Chronic kidney disease; DM, diabetes mellitus; HTN, hypertension.

Table 8a. Association between sleep disordered breathing/sleep apnea and all-cause death

Association between Central sleep apnea and all-cause death in the cohort				
	Unadjusted Model HR (95% CI)	Multivariate adjusted model1 HR (95% CI)	Multivariate adjusted model2 HR (95% CI)	Multivariate adjusted model3 HR (95% CI)
CSA(vs non-CSA)	7.379 (2.878-18.917)	3.621 (1.354-9.684)	3.621 (1.354-9.684)	4.642 (1.749-12.322)
Model 1 was adjusted for age, sex, BMI, CSA, OSA extend, NH, and RDI. Model 2 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, and HTN. Model 3 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, HTN, anti-HTN drugs, OHA, bilirubin and cholesterol.				
DM subjects				
CSA(vs non-CSA)	14.69 (4.114-52.452)	10.307 (2.288-46.437)	10.307 (2.288-46.437)	10.285 (2.285-46.281)
Model 1 was adjusted for age, sex, BMI, CSA, OSA extend, NH, and RDI. Model 2 was adjusted for age, sex, CSA, OSA extend, NH, RDI, and HTN. Model 3 was adjusted for age, sex, CSA, OSA extend, NH, RDI, HTN, anti-HTN drugs, bilirubin and cholesterol.				
HTN subjects				
CSA(vs non-CSA)	12.503 (3.908-40.007)	6.761 (1.862-24.554)	5.721 (1.52-21.528)	5.797 (1.558-21.574)

Model 1 was adjusted for age, sex, BMI, CSA, OSA extend, NH, and RDI. Model 2 was adjusted for age, sex, CSA, OSA extend, NH, RDI, and DM. Model 3 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, OHA, bilirubin and cholesterol.				
Overweight/obese subjects				
CSA(vs non-CSA)	9.735 (3.318-28.566)	5.345 (1.881-15.187)	5.345 (1.881-15.187)	7.317 (2.535-21.124)
Model 1 was adjusted for age, sex, BMI, CSA, OSA extend, NH, and RDI. Model 2 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, and HTN. Model 3 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, HTN, anti-HTN drugs, OHA, bilirubin and cholesterol.				
CKD subjects				
CSA(vs non-CSA)	9.933 (2.490-39.623)	9.901 (2.353-41.661)	7.09 (1.616-31.109)	11.093 (2.671-46.069)
Model 1 was adjusted for age, sex, BMI, CSA, OSA extend, NH, and RDI. Model 2 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, and HTN. Model 3 was adjusted for age, sex, CSA, OSA extend, NH, RDI, DM, HTN, anti-HTN drugs, OHA, bilirubin and cholesterol.				

Abbreviations: CI, confidence interval; CSA, central sleep apnea; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; MSA, mixed sleep apnea; OSA, obstructive sleep apnea; RDI groups, respiratory disturbance index >5/h, 15/h, and 30/h; CVD, cerebrovascular disease; CHD, coronary heart disease; OHA, oral hypoglycemic agents; BMI, body mass index.

In non-CSA subjects, the results from a model adjusted for traditional risk factors/predictors indicated that the obstructive AI-to-RDI ratio predicted the risk of death [adjusted HR = 1.015 (1.002-1.028), p = 0.033]. The obstructive AI-to-RDI ratio was also a predictor of mortality in DM subjects [adjusted HR = 1.053 (1.01-1.099), p = 0.016] and HTN subjects [adjusted HR = 1.036 (1.008-1.064), p = 0.01]. In patients with CKD, RDI was a risk factor for mortality [adjusted HR = 1.063 (1.005-1.123), p = 0.032]. However, instead of SDB/SA, age [adjusted HR = 1.102 (1.056-1.149), p < 0.001] was a risk factor for ACM in overweight/obese patients (Table 8b).

Table 8b. Association between sleep disordered breathing/sleep apnea and all-cause death in subjects without central sleep apnea

Association between SDB/SA and all-cause death in the cohort excluded CSA subjects.		
	Unadjusted Model HR (95% CI)	Fully-adjusted model HR (95% CI)
Obstructive AI-to-RDI ratio (+1%)	1.007 (0.995-1.019)	1.015 (1.002-1.028)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, central AI, mixed AI, obstructive AI, central AI-to-RDI ratio, obstructive AI-to-RDI ratio, mixed AHI-to-RDI ratio, age, BMI, gender, DM, HTN, CVD, CHD, anti-HTN, anti-platelet, anti-lipid, OHA, serum albumin, bilirubin, alkaline phosphatase, and hemoglobin.		
DM subjects.		
Obstructive AI-to-RDI ratio (+1%)	1.033 (1.002-1.064)	1.053 (1.01-1.099)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, central AI, mixed AI, obstructive AI, central AI-to-RDI ratio, obstructive AI-to-RDI ratio, mixed AHI-to-RDI ratio, age,		

BMI, gender, HTN, CVD, CHD, anti-HTN, anti-platelet, anti-lipid, serum albumin, bilirubin, alkaline phosphatase, and hemoglobin.		
HTN subjects.		
Obstructive AI-to-RDI ratio (+1%)	1.023 (1.001-1.046)	1.036 (1.008-1.064)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, central AI, mixed AI, obstructive AI, central AI-to-RDI ratio, obstructive AI-to-RDI ratio, mixed AHI-to-RDI ratio, age, BMI, gender, DM, CVD, CHD, anti-platelet, anti-lipid, OHA, serum albumin, bilirubin, alkaline phosphatase, and hemoglobin.		
CKD subjects.		
RDI (+1event/h)	1.016 (0.98-1.054)	1.063 (1.005-1.123)
Fully-adjusted model was adjusted for OSA extend, RDI groups, RDI, central AI, mixed AI, obstructive AI, central AI-to-RDI ratio, obstructive AI-to-RDI ratio, mixed AHI-to-RDI ratio, SaO2 (lowest, basal, average), SaO2 90% index, age, BMI, gender, DM, HTN, CVD, CHD, anti-HTN, anti-platelet, OHA, serum albumin, bilirubin, alkaline phosphatase, baseline eGFR, follow-up eGFR and hemoglobin.		

Abbreviations: CI, confidence interval; HR, hazard ratio; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; RDI, respiratory disturbance index ;RDI groups, RDI >5/h, 15/h, and 30/h. DM, diabetes mellitus; HTN, hypertension; CVD, cerebrovascular disease; CHD, coronary heart disease; OHA, oral hypoglycemic agents.

Chapter 4. Discussion

In the present study, CKD was associated with severe SDB (RDI

≥ 30/h). When MSA was considered a variant of clinical OSA, CSA was a risk factor for RDeG in the cohort, and was more evident in DM, HTN, or overweight/obese subjects, whereas OSA was a risk factor for RDeG in CKD patients. CSA was also a risk factor for ACM in the cohort, and was more evident in patients with DM, HTN, CKD, and those who were overweight/obese. After excluding patients with CSA, SDB/SA remained a predictor/risk factor for RDeG in the new cohort and in patients with CKD or who were overweight/obese. SDB/SA was also a risk factor for ACM in the new cohort and in patients with DM/HTN/CKD.

In this study, CKD participants tended to be older males with more comorbidity, worse sleep architecture, and more often had SDB with higher central AI and HI than non-CKD patients. All of these findings are mostly in agreement with previous studies (18-22). Patients with CKD had a higher prevalence of severe SDB (RDI ≥ 30/h) than those without CKD after adjusting for a wide spectrum of potentially relevant confounders. This finding is also in line with a previous study (25). Furthermore, In the Cox regression analysis of the cohort, we found that RDI was a predictor/risk factor for RDeG in the adjusted model. Consequently, these findings bring to light the possible harmful effect of SDB/SA on renal function, even in the absence of other traditional risk factors. A previous longitudinal population-based cohort study provided evidence that patients with OSA, even those without DM or HTN, are at a higher risk of developing CKD than a non-OSA cohort (38). Presence of OSA was not associated with a faster decline of graft function in kidney transplant recipients (36). However, in our study, we found that OSA was a risk factor for the rapid decline of renal function in non-dialysis CKD patients. Renal function in non-dialysis CKD patients with OSA should be routinely checked and timely intervention should be considered in order to prevent progression to ESRD. Despite classification of MSA as a variant of OSA, CSA was a risk factor for RDeG in the cohort and in patients with DM, HTN, CKD, and those who were overweight/obese. The

pathophysiological link between OSA and CKD has been studied extensively (39), but there remains a scarcity of literature on the relationship between CSA and CKD. Central sleep apnea is associated with increased sympathetic activation, vagal withdrawal, altered hemodynamic loading conditions, and hypoxemia, all of which aggravate heart failure, on the other hand, chronic heart failure (CHF) and interstitial pulmonary edema lead to central sleep apnea and periodic breathing (40), which would result in a positive feedback loop. Heart failure causes kidney dysfunction, and has a possible mechanism of low cardiac output, increased venous congestion and renal venous pressure, neurohormonal and inflammatory activation, and local changes, such as adenosine release (41). In the present study, we did not obtain data on heart function, which could have contributed to the investigation of the relationship between CSA and renal function. Hence, for a better investigation of the impact of SDB/SA on renal function, patients with CSA were excluded. In non-CSA patients, RDI was still a risk factor for RDeG in the new cohort and in patients with CKD and who were overweight/obese, but not in patients with DM/HTN. Intermittent hypoxia can induce HTN (42), impair insulin sensitivity (43), and is associated with an increased risk of developing type 2 DM (44). The impact of SDB/SA on renal function in non-CSA patients may be masked by intermittent hypoxia-induced HTN/DM. However, further research is needed to reveal the mechanism of this causal relationship. SDB/SA was a risk factor for the rapid decline of renal function; therefore, renal function changes should be monitored in patients who have SDB/SA.

SDB was shown to be related to cardiovascular and all-cause mortality (CVM and ACM) in a population-based study, and the adjusted HRs of severe SDB (AHI ≥ 15/h) for CVM and ACM are 3.8 (95% [CI] = 1.6 – 9.0) and 5.2 (95% [CI] = 1.4 – 19.2), respectively, after excluding those who received continuous positive airway pressure (CPAP) treatment (45). In the present study, twenty-six (3.2%) patients with an RDI ≥ 15/h died, while

12 patients (1.9%) with an RDI < 15/h died. No significant difference in the death rate was observed between RDI severities. CSA was an independent risk factor for ACM in the cohort. There are several reasons justifying the role of CSA as an independent risk for ACM in our cohort. During the follow-up period, 15.2% patients with CSA and 2.6% patients with OSA extend died. Patients with CSA had a higher mortality rate versus the OSA extend patients. Compared to non-CSA, participants with CSA were more likely to possess confounding factors such as HTN (48.5% versus 27.2%, p = 0.007), DM (24.2% vs. 12%, p = 0.035), and cerebrovascular disease (15.2% vs. 4.6%, p = 0.006). Patients with CSA may have experienced severe hypoxemia compared to non-CSA patients (SaO_2 = 93.8 ± 3.1% vs. 95.1 ± 3.4%, p = 0.0034; SaO_2 time < 90% = 12.6 ± 17.4 h vs. 5.6 ± 12.9 h, p = 0.002) (Table S1). Hypoxia may be the force that drives CKD (46). Moreover, SA may have potentially harmful effects on renal function. CSA was related to RDeG (adjusted HR = 2.238, [CI] 1.046-4.787), p = 0.038) without adjusting for MSA. When MSA was considered a variant of OSA, CSA was related to RDeG. Moreover, RDeG was found to be related to ACM (adjusted HR = 3.081 (1.059-8.965), p = 0.039) (Table S2). Thus, CSA may have increased ACM in our cohort through rapid worsening of renal function. All of these results partially explain the higher rate of ACM in patients with CSA.

Table S1. Baseline parameters of patients with and without central sleep apnea

	Non-CSA	CSA	p-value
Number	1415	33	
Age (years)	53.6 ± 13.6	59.1 ± 17.2	0.079
Male (%)	72.3	93.9	*0.005*
BMI (kg/m^2)	25.7 ± 3.8	26.3±3.5	0.376

Neck circumference (cm)	37.7 ± 11.3	39.0 ± 3.8	0.552
Waist to Hip ratio	1.10 ± 3.61	0.95 ± 0.05	0.892
GFR (ml/min/1.73 m2)	88.0 ± 18.5	81.6 ± 26.1	0.169
Comorbidity			
Hypertension (%)	27.2	48.5	*0.007*
Diabetes mellitus (%)	12	24.2	*0.035*
Coronary heart disease (%)	4.9	3	1
Cerebrovascular disease (%)	4.6	15.2	*0.006*
Cancer (%)	8.5	12.1	0.522
Sleep architecture			
Sleep efficiency (% TST)	79.9 ± 13.4	78.1 ± 14.9	0.428
Stage 1 (% TST)	13.5 ± 8.9	22.9 ± 17.3	*0.004*
Stage 2 (% TST)	50.2 ± 12.8	38.2 ± 17.9	*0.001*
SWS (% TST)	5.6 ± 6.8	3.8 ± 6.8	0.143
REM (% TST)	14.9 ± 7.5	15.7 ± 10.2	0.65
Respiratory arousal (/hr)	17.9 ± 19.5	37.5 ± 19.8	*<0.001*
RDI (/hr)	24.5 ± 22.6	52.0 ± 18.6	*<0.001*
Apnea index AI(/hr)	13.6 ± 19.2	37.6 ± 19.8	*<0.001*
Central AI (/hr)	0.3 ± 0.6	10.5 ± 8.4	*<0.001*
Obstructive AI (/hr)	12.1 ± 17.5	15.9 ± 13.2	0.218
Mixed AI (/hr)	1.2 ± 4.6	13.6 ± 16.8	*<0.001*
Hyponea index (/hr)	11.0 ± 10.3	14.4 ± 12.1	0.121
Desaturation index (/hr)	19.1 ± 21.2	50.0 ± 19.2	*<0.001*
Average SaO_2 (%)	95.1 ± 3.4	93.8 ± 3.1	*0.034*
Lowest SaO_2 (%)	83.1 ± 8.4	76.2 ± 11.3	*0.002*
SaO_2 <90% (/hr)	5.6 ± 12.9	12.6 ± 17.4	*0.002*

Abbreviations: CSA, central sleep apnea; MSA, mixed sleep apnea; OSA, obstructive sleep apnea; RDI, respiratory disturbance index .

Table S2 Association between rapid decline of eGFR and all-cause death in the cohort

	Unadjusted Model HR (95% CI)	Fully-adjusted model HR (95% CI)
RDeG (vs Non-RDeG)	6.406 (2.599-15.79)	3.081 (1.059-8.965),

Fully-adjusted model was adjusted for age, sex, BMI, CSA, OSA extend, RDI groups, DM, HTN, anti-HTN drugs, OHA, alkaline phosphatase, and hemoglobin.

Abbreviations: CI, confidence interval; RDeG, rapid decline of eGFR; CSA, central sleep apnea; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; OSA, obstructive sleep apnea; RDI groups, respiratory disturbance index >5/h, 15/h, and 30/h. OHA, Oral hypoglycemic agents.

In the subgroups (DM/HTN/CKD/overweight/obese), CSA was a risk factor for ACM. The adjusted HR of CSA in the DM/HTN/CKD/overweight/obese population was higher than in the whole cohort. Therefore, CSA was a more pronounced mortality risk in patients with DM/HTN/CKD and those who were overweight/obese than in the whole cohort. Patients who experience predominate CSA may have severe CVD, which may contribute to ACM. Therefore, for a better investigation of the effects of SDB/SA on ACM, we excluded the CSA subjects from the cohort. In the cohort excluding CSA, we found that the obstructive AI-to-RDI ratio was a predictor of ACM in a fully adjusted model. The adjusted HR of the obstructive AI-to-RDI ratio was higher in patients with DM or HTN when compared with patients in the new cohort. In CKD subjects, RDI was a predictor of ACM. SDB/SA deserves more medical attention in patients with DM/HTN/CKD.

We acknowledge that there are limitations to this investigation. First, the present research was a relatively small, single-center study. The possibility of selection bias could not be eliminated. The size of the cohort was not large enough to control for all confounders, despite the fact that controlling for over-fitting was considered. Other confounders need to be addressed in future studies. The associations found in this study could be perceived as a hypothesis. Larger multi-center investigations are needed in order to collect data to support the associations. Second, the diagnosis dates of the participants were not reflective of SDB/SA onset. Thus, the impact of SDB/SA on CKD might be underestimated. Third, we did not have access to detailed death records, which may have clarified the association between SDB/SA and ACM. Additional studies with greater power are needed to uncover the reasons. Fourth, the cases for the analysis of renal outcome may be insufficient; however, the analysis of renal outcome was used to help explain the effect of SDB/SA on ACM. Animal experiments may be needed to uncover the pathophysiological effects of SA on renal function.

Chapter 5. Conclusions

In our study, CKD was found to be associated with severe SDB (RDI ≥ 30/h). SDB/SA was a predictor/risk factor for the rapid

decline of eGFR in the cohort and in subjects who had CKD or were overweight/obese. SDB/SA also predicted the risk of death in the cohort and in HTN/DM/CKD subjects.

Screening for SDB/SA should be considered for DM/HTN/CKD patients, and timely intervention should be performed to reduce the mortality risk.

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국문초록

수면호흡장애/수면무호흡증과 신장기능의 변화 및 사망률의 관계 연구: 수면클리닉 코호트 연구

배경: 수면호흡장애(SDB)/수면성 무호흡(SA)의 만연함은 높다. SDB/SA와 만성 신부전(CKD)은 많은 위험성인 변리생리적 매캐니즘을 공유한다, 그리고 흔히 진성 당뇨병 (DM), 고혈압 (HTN), 체질량 지수 내 과체중/비만 범위(≥ 23 kg/m 2)와 동반이환된다. 이전의 연구는 거의 SDB/SA와 신기능의 상관관계에 집중해왔다. 현재의 연구는 SDB/SA가 DM, HTN, CKD, 과체중/비만이있는 환자들의 신장 기능 쇠퇴에 미치는 영향에 대해서 연구했다. 사구체 여과 속도 추정(eGFR; RDeG)의 급속한 감속은 전 원인 사망률의 (ACM)의 위험요소라 알려졌다; 그러므로, ACM에대한 SDB/SA의 영향 또한 연구되었다.

연구방법: 저희는 수면 클리닉의 종단 연구를 수행하였다. 분석연구 I 에서 2007년 5월 에서 7월 2014년사이 SDB/SA에대한 진단시험을 추천 받고, 수면다원검사을 받았으며, 검사결과에 에서의 혈청 크레아티닌 레벨이 있는 모든 성인대상들을 등록하였고 지켜보았다. 분석연구 II 에서는, 뚜렷한 중추수면무호흡(CSA)이 있는 환자들은 흔히 심장병 또는 뇌혈관질환과 동반이환되어 더 높은 사망률이 있을 수 있기 때문에, 이 환자들은 분석연구 I 에서 제외되었다. 두 연구의 측정된 결과 모두 ACM과 RDeG 이었다.

결과: 총 1454명의 참가자가 분석연구 I 에 포함되었다. 이 중, 103명의 환자(7.08%) 가 CKD가 있었고 38명의 환자(2.61%)가 연구 도중 사망하였다. CKD는 극심한 SDB [오즈비(OR) = 1.74 (1.12−2.70), p < 0.05] 와 연관되었다. CSA는 집단중 RDeG, [조정된 위험 비율 (HR) = 2.451 (1.193−5.037), p = 0.015], DM 대상 [조정된 위험 비율 = 2.951 (1.032−8.434), p = 0.043], HTN 대상 [조정된 위험 비율 = 2.524 (1.146−5.558), p = 0.022] 그리고 과체중/비만 대상 [조정된 위험 비율 = 3.207 (1.528−6.73), p = 0.002]과 연관되었다.

폐쇄수면무호흡 (OSA)은 CKD 환자들의 RDeG에대한 위험요소였다 [조정된 위험 비율 = 3.242 (1.235−8.51), p = 0.017]. CSA는 집단의 ACM [조정된 위험 비율 = 4.642 (1.749−12.322), p = 0.002], DM [조정된 위험 비율 = 10.285 (2.285−46.281), p = 0.002], HTN [조정된 위험 비율 = 5.797 (1.558−21.574), p = 0.009], CKD [조정된 위험 비율 = 11.093 (2.671−46.069), p = 0.001], 그리고 과체중/비만 대상 [조정된 위험 비율 = 7.317 (2.535−21.124), p < 0.001] 에대한 위험요소였다. 연구결과 II 에서는, 호흡장애지수 (RDI)가 집단의 RDeG [조정된 위험 비율 = 1.007 (1−1.015), p = 0.047], CKD 대상[조정된 위험 비율 = 1.038 (1.001−1.075), p = 0.043], 그리고 과체중/비만 대상 [조정된 위험 비율 = 1.011 (1.004−1.019), p = 0.005] 에대한 위험요소라는걸 찾아내었다. 호흡장애지수 (RDI) -에- 무호흡장애지수 (AI) 비율은 집단의 사망위험률을 예견하였다 [조정된 위험 비율 = 1.015 (1.002−1.028), p = 0.033], DM 대상[조정된 위험 비율 = 1.053 (1.01−1.099), p = 0.016], 그리고 HTN 대상 [조정된 위험 비율 = 1.036 (1.008−1.064), p = 0.01], 반면 RDI는 CKD대상의 ACM에대한 위험요소였다. [조정된 위험 비율 = 1.063 (1.005−1.123), p = 0.032].

결론: 현재 연구에서, CKD는 극심한 SDB (RDI ≥ 30/h)와 연관되었다. SDB/SA는 집단과 CKD가있는 환자들, 혹은 과체중/비만인 자들의 eGFR에대한 급속한 감소의 전조/위험 요소였다. SDB/SA 또한 집단과 HTN/DM/CKD가 있는 환자들의 사망 위험률을 예견하였다. 사망률을 낮추기 위해선 DM/HTN/CKD 환자들의 SDB/SA에대한 다중단계 접근법을 사용하는 다양한 치료양식을 추천한다.

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주요어: 수면무호흡증; 만성 신부전; 전 원인 사망률; 수면호흡장애; 신장 기능 쇠퇴

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