Urinary 8-OxoGsn as A Potential Indicator of Mild Cognitive Impairment in Frail Patients With Cardiovascular Disease

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Research Article

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Abstract

Background

Oxidative RNA damage has been found to be associated with age-related diseases and 8-oxo-7,8-dihydroguanosine (8-oxoGsn) is a typical marker of oxidative modification of RNA. We aimed to assess whether the measurement of urinary 8-oxoGsn could represent a potential early maker in mild cognitive impairment (MCI) among frail patients with cardiovascular disease (CVD).

Methods

Urinary 8-oxoGsn was measured in frail (Fried phenotype: 3–5) inpatients with CVD and was corrected by urinary creatinine (Cre) levels. Cognitive function was assessed by the Mini-Mental State Examination (MMSE), participants were classified into non-MCI (≥ 24) and MCI (< 24). Univariate and multivariable logistic regression models were used to determine the relationship between 8-oxoGsn/Cre and MCI. Receiver operating characteristic (ROC) curve analysis was used to assess the 8-oxoGsn/Cre ratio in relation to MCI in frail patients with CVD.

Results

A total of 106 elderly patients were enrolled in this study. The mean age of participants was 77.9 ± 6.8 years, the overall prevalence of MCI was 22.6% (24/106). In the multivariate logistic regression analysis, urinary 8-oxoGsn/Cre was independently associated with MCI (odds ratio [OR] = 1.769, 95% confidence interval [CI] = 1.234–2.536, p = 0.002), after adjusting for age, sex, education level, marital status, and serum prealbumin levels. The area under the ROC curve was 0.786 (0.679–0.893) (p < 0.001), and the optimal cut-off value was 4.22 µmol/mol. The urinary 8-oxoGsn/Cre ratio showed a sensitivity of 87.5% and a specificity of 69.5%.

Conclusion

The present study suggests the urinary 8-oxoGsn/Cre ratio may be a useful indicator for the early screening of MCI in frail patients with CVD.

Trial registration:

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Mild cognitive impairment (MCI) is a transition between normal aging and dementia, and is an early indicator of dementing disorders in adults[1]. It has been estimated that subjects with MCI have a 10-fold increased risk of developing Alzheimer's disease (AD) at a rate of 15% annually[2]. Distinguishing between the MCI individuals from general individuals is an important task. A complete understanding of risk factors and biomarkers is required for early detection of MCI.

In older adults, frailty represents a state of increased vulnerability to stressor events and increases the risk of early mortality, disability, falls, and hospitalization[3]. Frailty is common in patients with cardiovascular disease (CVD) and is associated with an increased risk. There is a bidirectional link between frailty and CVD[4], in which frailty is associated with an earlier onset of CVD, and conversely the presence of CVD is associated with a greater incidence of frailty[5]. These two disease states influence each other and worsen the prognosis of these patients. Frail patients with CVD have been associated with a significantly increased risk of developing vascular dementia than non-frail patients[6]. Early detection of MCI can help to prevent vascular dementia in frail patients with CVD.

The most commonly used markers of frailty and MCI are those related to inflammatory, nutritional, vascular, and metabolic factors[7]. In addition, frailty and cognitive decline are associated with oxidative stress, a pro-inflammatory environment with increased oxidative stress leading to endothelial dysfunction, which links MCI and frailty[8].

We and other groups have found that oxidative stress contributes significantly to the pathogenesis and progression of AD[9, 10], as well as other forms of dementia[11]. Oxidative RNA damage can impair protein translation, and the damaged RNA can be prematurely degraded, further impairing the synthesis of essential proteins[12]. The oxidative stress marker 8-oxo-7,8-dihydroguanosine (8-oxoGsn) can reliably be quantified in urine using an ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) assay and is a valid marker of RNA damage[13]. Central 8-oxoGsn may be associated with the pathogenesis of bipolar disorder[14], which is a mental disorder characterized by recurrent relapses of affective episodes, cognitive impairment, and illness progression[15]. In a study of 5 patients with MCI, increased oxidative modification of RNA was found in neurons formed by early neurofibrillary tangles in the hippocampus/parahippocampal gyrus[1]. However, these examinations are invasive, both requiring sampling of the cerebrospinal fluid and the hippocampus. In the realm of biomarker discovery, the urine has been a popular matrix due to its noninvasive collection in humans and its availability in large quantities[16], it provides a precious clinical sample for early noninvasive disease diagnosis. If patients with MCI could be detected early by examination of urine, the burden on patients will be reduced.

Our previous study showed that urinary 8-oxoGsn is independently associated with frailty in elderly patients with CVD[17]. However, only a few studies have investigated RNA oxidation and MCI in frail patients with CVD. The aim of this study was to assess whether 8-oxoGsn could represent a potential early maker in AD development among frail patients with CVD.

**Methods**
Study design and participants

This study was a prospective cross-sectional study performed in China, which included inpatients aged ≥ 65 years old admitted to the Department of Cardiology from September 2018 to February 2019. Baseline assessments were carried out by experienced and trained investigators. Written informed consent was obtained from all participants. The study was reviewed and approved by the Ethics Committee. For the current study, participants were included if they met the following conditions: (1) definite diagnosis of CVD; (2) frail patients: Fried phenotype ≥ 3; and (3) sufficient urine samples for analysis. Participants were excluded from this study if they had a definite diagnosis of AD. Initially, 542 individuals with CVD participated in the baseline study. We excluded 348 robust and 64 pre-frail participants. In addition, 24 participants without fresh urine samples were excluded, including 1 patient with AD. Finally, this study enrolled 106 participants for the analysis of whether 8-oxoGsn is a useful marker for MCI in frail patients with CVD.

Assessment of frailty

The Fried phenotype was used to assess frailty. It was defined according to the definition proposed by Fried et al.[3] based on five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Participants meeting three or more criteria were categorized as frail according to the following criteria:

1. unintentional weight loss: weight decreased by > 5% in the previous year;
2. self-reported exhaustion: feeling tired all of the time (at least 3 or 4 days per a week);
3. weakness: maximum grip strength of the dominant hand at ≤ 20% of the population distribution, adjusted for sex and body mass index;
4. slow walking speed: using the average of timed walk test over a 4-meter course, defined as walking 4-meter at < 0.65m/s (height ≤ 173 cm for men or ≤ 159 cm for women) or < 0.76 m/s (height > 173 cm for men or > 159 cm for women);
5. low physical activity: <383 kcal per week for men or < 270 kcal per week for women.

Cognitive function assessment

Cognitive function was assessed by the Chinese version of the Mini-Mental State Examination (MMSE) [18]. The MMSE tests consists of 30 items within 6 dimensions: orientation, registration, attention, language, memory, and visual construction skills[19]. The total MMSE score ranged from 0 to 30, with higher scores reflecting better cognitive function. We treated responses of “unable to understand and answer” as “wrong”[20]. Participants were classified into non-MCI (NO-MCI, ≥ 24) and MCI (< 24) using the cut-off score of 24.

Measurement of urinary 8-oxoGsn and creatinine in all patients
For this study, fresh midstream urine samples were obtained in the morning within 24 h after admission to hospital. All samples were coded at the moment of collection to ensure a blind study. Urine samples were stored at -80°C until they were processed. The samples were thawed at 4°C, then after centrifugation at 7500 · g for 5 min to remove large particles, the supernatant was used for the analysis. Urinary 8-oxoGsn levels were determined by UPLC-MS/MS, as described in full detail elsewhere[17]. Creatinine (Cre) concentrations were determined in urine samples with the MicroVue Creatinine EIA kit (Hitachi koki; Tokyo, Japan). The results for 8-oxoGsn in urine were normalized for Cre.

**Statistical analyses**

The Kolmogorov-Smirnov test was used to verify whether continuous variables conformed to a normal distribution. Results were expressed as mean and standard deviation (normally distributed data) or median (interquartile range; non-normally distributed data). Categorical variables were expressed as numbers and percentages. The Student t-test or Mann-Whitney test for continuous data and the Fisher exact test or chi-square test for categorical data were used to identify statistical differences between the two groups. In our study, prealbumin was used to reflect nutritional status and high-sensitivity C-reactive protein was used to represent inflammatory state, which are commonly used markers of MCI. Univariate and multivariable logistic regression models were used to determine the relationship between the 8-oxoGsn/Cre ratio and MCI. Multivariable logistic regression was adjusted for age, sex, education level, marital status, and serum prealbumin levels (factors with a p-value < 0.10 in univariate analyses were entered into the multivariate model). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the results of the logistic regression models. Receiver operating characteristic (ROC) curve analysis was used considering the 8-oxoGsn/Cre ratio in relation to MCI in frail patients with CVD. The optimal cutoff point was calculated using the maximum value of the Youden Index (determined as sensitivity+[1-specificity])[17]. A p-value < 0.05 was considered statistically significant. All the data analyses were conducted using the IBM SPSS Statistics software program (version 24; IBM Corporation, Armonk, NY, USA). Graphs were created with GraphPad Prism version 7.0.0 for Windows (GraphPad Software San Diego, CA, USA).

**Results**

The characteristics of the study population are presented in Table 1. Overall, a total of 106 elderly frail patients were enrolled in this study. The participants were classified into NO-MCI (n = 82) and MCI (n = 24) groups based on the MMSE scores. At baseline, the mean age of participants was 77.9 ± 6.8 years, 57.5% (61/106) of participants were women. Age (p < 0.001), sex (p = 0.003), education level (p < 0.001), and marital status (p = 0.007) showed statistically significant differences between groups. Among the five criteria of frailty, the MCI group had more patients exhibiting weakness (p = 0.029) compared to the NO-MCI group, no significant differences were observed regarding the proportion of individuals with unintentional weight loss (p = 0.183), self-reported exhaustion (p = 0.096), slow walking speed (p = 0.936), and low physical activity (p = 0.975). Furthermore, there were no differences in comorbidities or serum high sensitivity C-reactive protein levels among the two groups. Serum prealbumin was slightly higher in
NO-MCI cases than in MCI cases (22.75 ± 5.11 vs. 19.04 ± 5.74 mg/dL; p = 0.003). Participants with MCI were more likely to have higher levels of urinary 8-oxoGsn/Cre (5.43 [4.39–6.38] vs. 3.60 [2.94–4.42] µmol/mol; p < 0.001) (Fig. 1).

Table 1
The baseline characteristics of study participants by cognitive function status.

|                          | Overall (n = 106) | NO-MCI (n = 82) | MCI (n = 24) | P   |
|--------------------------|-------------------|-----------------|--------------|-----|
| Age, year                | 77.9 ± 6.8        | 76.7 ± 6.8      | 82.2 ± 5.2   | <0.001 |
| Sex, female (%)          | 61(57.5)          | 41(50.0)        | 20(83.3)     | 0.003  |
| Education level, year    | 10(9–15)          | 12(9–15)        | 6(1–11)      | <0.001 |
| Married (%)              | 83(78.3)          | 69(84.1)        | 14(58.3)     | 0.007  |
| MMSE                     | 28(24–29)         | 28(27–29)       | 20(13–23)    | <0.001 |
| Unintentional weight loss (%) | 34(32.1)       | 29(35.4)        | 5(20.8)      | 0.183  |
| Self-reported exhaustion (%) | 94(88.7)       | 75(91.5)        | 19(79.2)     | 0.096  |
| Weakness (%)             | 85(80.2)          | 62(75.6)        | 23(95.8)     | 0.029  |
| Slow walking speed (%)   | 88(83.0)          | 68(82.9)        | 20(83.3)     | 0.963  |
| Low physical activity (%) | 97(91.5)         | 75(91.5)        | 22(91.7)     | 0.975  |
| Prealbumin, mg/dL        | 21.90 ± 5.46      | 22.75 ± 5.11    | 19.04 ± 5.74 | 0.003  |
| High sensitivity C-reactive protein, mg/L | 1.28(0.58–4.68) | 1.14(0.54–4.50) | 1.70(0.59–11.23) | 0.269  |
| Coronary artery disease (%) | 59(55.7)        | 45(54.9)        | 14(58.3)     | 0.767  |
| Hypertension (%)         | 79(74.5)          | 60(73.2)        | 19(79.2)     | 0.558  |
| Heart failure (%)        | 22(20.8)          | 16(19.5)        | 6(25.0)      | 0.564  |
| Atrial fibrillation (%)  | 36(34.0)          | 26(31.7)        | 10(41.7)     | 0.370  |
| Diabetes (%)             | 45(42.5)          | 38(46.3)        | 17(70.8)     | 0.137  |
| Previous stroke (%)      | 25(23.6)          | 16(19.5)        | 9(37.5)      | 0.069  |
| Obesity (%)              | 23(21.7)          | 19(23.2)        | 4(16.7)      | 0.501  |

Note. NO-MCI = Non mild cognitive impairment; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; Cre = creatinine.

Values are shown as mean ± standard deviation or median (interquartile range) or n (%).
Univariate analysis demonstrated that age (p = 0.001), sex (p = 0.006), education level (p < 0.001), marital status (p = 0.009), serum prealbumin (p = 0.005), and urinary 8-oxoGsn/Cr (p = 0.005) were associated with MCI. To better explore the association between 8-oxoGsn/Cr and MCI, a multivariate logistic regression model was built. The urinary 8-oxoGsn/Cr ratio was independently associated with MCI (OR = 1.769, 95% CI = 1.234–2.536, p = 0.002), after adjusting for age, sex, education level, marital status, and serum prealbumin. Age (OR = 1.202, 95% CI = 1.045–1.383, p = 0.010) and education level (OR = 0.742, 95% CI = 0.621–0.886, p = 0.001) were independently associated with MCI among frail patients with CVD (Table 2).
Table 2
Univariate and multivariate logistic regression.

| Variables                              | Univariate analysis |          |          |          | Multivariate analysis |          |          |          |
|----------------------------------------|---------------------|----------|----------|----------|-----------------------|----------|----------|----------|
|                                        | OR                  | 95%CI    | P        | OR       | 95%CI     | P        |
|                                        | Lower               | Upper    |          | Lower    | Upper     |          |
| Age, year                              | 1.144               | 1.056    | 1.240    | 0.001    | 1.202     | 1.045    | 1.383    | 0.010    |
| Female                                 | 5.000               | 1.570    | 15.910   | 0.006    | 0.290     | 0.059    | 1.424    | 0.127    |
| Higher level of education, year        | 0.724               | 0.626    | 0.836    | <0.001   | 0.742     | 0.621    | 0.886    | 0.001    |
| Married                                | 0.264               | 0.097    | 0.720    | 0.009    | 1.013     | 0.194    | 5.281    | 0.988    |
| Unintentional weight loss              | 0.481               | 0.163    | 1.422    | 0.186    | -         | -        | -        | -        |
| Self-reported exhaustion               | 1.027               | 0.199    | 5.302    | 0.975    | -         | -        | -        | -        |
| Weakness                               | 7.419               | 0.941    | 58.480   | 0.057    | -         | -        | -        | -        |
| Slow walking speed                     | 1.029               | 0.305    | 3.480    | 0.963    | -         | -        | -        | -        |
| Low physical activity                  | 0.355               | 0.101    | 1.242    | 0.105    | -         | -        | -        | -        |
| 8-oxoGsn/Cre, µmol/mol                 | 1.415               | 1.112    | 1.800    | 0.005    | 1.769     | 1.234    | 2.536    | 0.002    |
| Prealbumin, mg/dL                      | 0.876               | 0.798    | 0.962    | 0.005    | 0.904     | 0.793    | 1.031    | 0.133    |
| High sensitivity C-reactive protein, mg/L | 1.018              | 0.979    | 1.059    | 0.362    | -         | -        | -        | -        |
| Coronary artery disease                | 1.151               | 0.458    | 2.891    | 0.765    | -         | -        | -        | -        |
| Hypertension                           | 1.393               | 0.464    | 4.184    | 0.554    | -         | -        | -        | -        |
| Heart failure                          | 1.375               | 0.470    | 4.022    | 0.561    | -         | -        | -        | -        |
| Atrial fibrillation                    | 1.538               | 0.604    | 3.920    | 0.367    | -         | -        | -        | -        |
| Diabetes                               | 0.477               | 0.179    | 1.272    | 0.139    | -         | -        | -        | -        |
| Previous stroke                        | 2.475               | 0.919    | 6.665    | 0.073    | -         | -        | -        | -        |

Note. OR = odds ratio; CI = confidence interval; 8-oxoGsn = 8-oxo-7,8-dihydroguanosine; Cre = creatinine.
### Variables

| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|-----------------------|
| Obesity   | 0.663 0.202 2.179   | 0.499 - - - -         |

Note. OR = odds ratio; CI = confidence interval; 8-oxoGsn = 8-oxo-7,8-dihydroguanosine; Cre = creatinine.

A ROC curve analysis was performed to estimate the diagnostic potential of urinary the 8-oxoGsn/Cre ratio for MCI. The area under the ROC curve (AUC) was 0.786 (0.679–0.893) (p < 0.001) (Fig. 2). The optimal cut-off value of the urinary 8-oxoGsn/Cre ratio by the maximal Youden index was 4.22 µmol/mol. It showed a sensitivity of 87.5% and a specificity of 69.5%. Its positive predictive and negative predictive values were 74.2% and 84.8%, respectively, and its positive likelihood ratio and negative likelihood ratio were 2.87 and 0.18.

### Discussion

In this cross-sectional study, we reported the overall prevalence of MCI among frail patients with CVD was 22.6%, which was similar to previous findings[22]. We confirmed that urinary 8-oxoGsn/Cre ratios were significantly higher in MCI patients compared to NO-MCI patients (p < 0.001). Urinary 8-oxoGsn/Cre could independently and effectively evaluate MCI in frail patients with CVD.

The use of feasible biomarkers to identify patients with MCI is a challenge that needs to be addressed: These indicators would provide a more accurate detection of AD in early disease stages, when cognitive decline can still be potentially reverted. For the development of MCI related biomarkers, physiological and metabolic processes, changes in MCI status must be explored. Individuals with MCI have shown alterations in the antioxidant system, which is designed to counteract the potentially hazardous reactions initiated by oxidative stress[23]. Nucleic acids are constantly oxidized within the cell, DNA is double stranded and contains protective proteins. Pena-Bautista et al. showed the DNA oxidation marker 8-hydroxy-2'-deoxyguanosine was able to distinguish between AD and healthy participants[24]. However, RNA is more vulnerable to oxidative stress than DNA because it is single-stranded and lacks protective histones[25]. RNA damage is a valid marker that may be suitable to provide useful information for early identification of MCI. The oxidatively generated modifications of RNA can be measured by urinary 8-oxoGsn levels[26], which is the focus of the present study.

Our study found that urinary 8-oxoGsn corrected by creatinine was independently associated with MCI. Previous studies on oxidative stress and cognitive impairment have mainly focused on brain tissue and cerebrospinal fluid rather than on urine samples. Urine is a valuable clinical specimen for early noninvasive diagnosis of diseases. However, these studies have mainly focused on the relationship between oxidative stress and dementia or AD, which are already irreversible. Nunomura et al. suggested that RNA oxidation is a prominent feature of neuronal vulnerability in patients with AD[27] and dementia[28]. Our previous research found that the presence of large amounts of 8-oxoGsn in the RNA
could promote the secretion of pathogenic amyloid-β peptides \textit{in vivo}\cite{10}, and the mechanism would contribute to the accumulation of amyloid-β plaques, as observed in the brains of AD patients. Consistent with previous data, Lovell et al. demonstrated increased RNA oxidative modifications in neurons undergoing early neurofibrillary tangles formation in the hippocampus/parahippocampal gyrus of MCI and late-stage AD subjects\cite{1}. Levels of RNA oxidative damage in MCI were comparable to those observed in late-stage AD\cite{1}, suggesting that oxidative damage is an early event in the pathogenesis of AD. These results indicated that 8-oxoGsn is correlated with certain late-stage chronic nervous system diseases that have a high incidence among elderly patients. MCI is an early stage of AD and can be well screened by the MMSE scale in elderly patients. A possible conclusion is therefore that 8-oxoGsn levels may be positively correlated with MCI, which also has a high incidence in the elderly patients, especially among those with CVD.

MCI reflects the transition between normal aging and dementia, and is the earliest clinical manifestation of AD. It is important to determine if oxidative stress is present in individuals early in chronic disease progression. Perez et al. found that titanium dioxide nanoparticles induced strong oxidative stress in astrocytes, cells that play key roles in neuronal homeostasis and their dysfunction can lead to MCI\cite{29}. Keller et al. showed significantly increased protein carbonyl formation and increased levels of lipid peroxidation in the temporal lobe of MCI subjects compared to healthy subjects\cite{30}. Ding et al. showed significantly elevated 8-hydroxyguanine immunoreactivity in the inferior parietal lobule of subjects early in disease progression\cite{31}. Our study suggests the increase of the urinary 8-oxoGsn/Cr ratio may be a useful indicator for the early screening of MCI.

The usual risk factors associated with conversion of individuals from cognitively normal status into dementia and AD are also possible risk factors for transitions into MCI\cite{32}. The findings that age and education levels were independently associated with MCI are consistent with the existing literature\cite{33, 34}. It is estimated that between 10–30% of all adults aged 65 and above experience MCI\cite{2}. In a longitudinal study at the University of Kentucky AD Center, it was shown that age affected the ORs of individuals transitioning to MCI as well as that of dementia or death\cite{32}. In an analysis of six international longitudinal studies, a higher level of education was associated with a lower risk of transitioning from NO-MCI to MCI. Moreover, those with higher levels of education and socioeconomic status had longer non-impaired life expectancies\cite{35}.

Cardiovascular risk factors are recognized as predictors of age-related cognitive decline and dementia\cite{36}. MCI is an important under-researched complication of stroke and transient ischemic attack\cite{37}. However, it is important to note that in frail patients with CVD, no clear correlation between CVD and MCI has been identified, including previous stroke history. These findings were not consistent with our hypothesis. One possible reason for this inconsistency may be that we excluded patients with AD from our study, and only patients with mild cognitive decline were enrolled, and thus there was an insufficient number of cases with CVDs to detect early changes in cognitive function. Second, previous studies have found that some CVDs and risk factors, such as heart failure\cite{38}, coronary artery disease\cite{39}, stroke\cite{40}, atrial fibrrillation\cite{41}, and obesity\cite{42}, are significantly associated with frailty, thus
the relationship between CVDs and MCI may be weakened in frail patients. Further research on CVDs and MCI in frail patients should be performed in the future.

The strengths of the current study include the analysis of oxidized nucleosides using UPLC-MS/MS, which is considered the reference standard method due to high specificity towards the RNA forms. Furthermore, we adjusted the association between 8-oxoGsn levels and frailty by including all frail patients. Moreover, we tried to extend the relationship between 8-oxoGsn and MCI to general CVDs rather than to a specific form of CVD.

Our study has several limitations. First, the small sample size hampers the generalizability of our findings. However, the individuals included in our study were all frail patients with CVD, which may more accurately reflect the value of 8-oxoGsn in this subset of the population. Second, our cross-sectional study does not allow to draw any causative conclusions, nor can it identify the risk factors of MCI. A long-term follow-up study in this population is currently being conducted by our group, which will allow us to determine whether these patients develop dementia or AD in the future. Lastly, MMSE is a screening tool to identify MCI but it is not a diagnostic tool; thus, we failed to conduct a detailed subgroup analysis of patients with different cognitive levels. Nonetheless, the MMSE is the most widely used tool for evaluating MCI, and is supported by a high degree of popularization and application.

Conclusions

The present study suggests the urinary 8-oxoGsn/Cre ratio may be a useful indicator for the early screening of MCI in frail patients with CVD. This indicator will enhance our understanding of the pathological processes involved in MCI and the potential risk factors for early AD progression. With the aging population, the number of frail patients with CVD may continue to increase. Early recognition of cognitive dysfunction and early intervention may help to improve the quality of life and prognosis of these patients.

List Of Abbreviations

MCI, Mild cognitive impairment;
AD, Alzheimer’s disease;
CVD, Cardiovascular disease;
oxGsn, 8-oxo-7,8-dihydroguanosine;
MMSE, Mini-Mental State Examination;
UPLC-MS/MS, Ultra-performance liquid chromatography-mass spectrometry;
NO-MCI, Non mild cognitive impairment;
Cre, Creatinine;  
OR, Odds ratio;  
CI, Confidence interval;  
ROC, Receiver operating characteristic curve;  
AUC, Area under the ROC curve.

Declarations

Ethics approval and consent to participate

All participants signed their informed consent according to the Declaration of Helsinki prior to data collection. This study was reviewed and approved by the Ethics Committee of Beijing Hospital, China. (ID number: 2018BJYYEC-121-02), the version date of the protocol approved by ethics is September 18, 2018, and the version number is 1.0.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Population Health Data Archive repository, [https://www.ncmi.cn/projectdata/data-indexProject.html?type=manager&id=526&active=fabushuju]

Conflicts of interest

Every author declares not to have any conflict of interest.

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Authors' contributions

WH, YJF and CJP designed research. YSM and ZPP contributed to the development of the conceptualization and methodology, and wrote the paper. WH, SN and YSM analyzed data. All of the authors read the draft, made contributions and approved the final manuscript.
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**Figures**
Figure 1

Boxplot for 8-oxoGsn/Cre in the urine samples of NO-MCI and MCI individuals. Error bars represent median with interquartile distance. Note. 8-oxoGsn=8-oxo-7,8-dihydroguanosine; Cre=creatinine; NO-MCI=Non mild cognitive impairment; MCI=mild cognitive impairment.

AUC=0.786, p<0.001

Figure 2

Receiver operating characteristic curve for the 8-oxoGsn/Cre to predict MCI. Note. 8-oxoGsn=8-oxo-7,8-dihydroguanosine; Cre=creatinine; MCI=mild cognitive impairment; AUC=areas under the curve.