A Multicentre Prospective Evaluation of the Impact of Renal Insufficiency on In-hospital and Long-term Mortality of Patients with Acute ST-elevation Myocardial Infarction

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Abstract

Background: Numerous previous studies have shown that renal insufficiency (RI) in patients with acute coronary syndrome is associated with poor cardiovascular outcomes. These studies do not well address the impact of RI on the long-term outcome of patients with acute ST-elevation myocardial infarction (STEMI) in China. The aim of this study was to investigate the association of admission RI and inhospital and long-term mortality of patients with acute STEMI.

Methods: This was a multicenter, observational, prospective-cohort study. 718 consecutive patients were admitted to 19 hospitals in Beijing within 24 hours of onset of STEMI, between January 1,2006 and December 31,2006. Estimation of glomerular filtration rate (eGFR) was calculated using the modified abbreviated modification of diet in renal disease equation-based on the Chinese chronic kidney disease patients. The patients were categorized according to eGFR, as normal renal dysfunction (eGFR $\geq$ 90 ml·min^{-1}·1.73 m^{-2}), mild RI (60 ml·min^{-1}·1.73 m^{-2} $\leq$ eGFR < 90 ml·min^{-1}·1.73 m^{-2}) and moderate or severe RI (eGFR < 60 ml·min^{-1}·1.73 m^{-2}). The association between RI and inhospital and 6-year mortality of was evaluated.

Results: Seven hundred and eighteen patients with STEMI were evaluated. There were 551 men and 167 women with a mean age of 61.0 ± 13.0 years. Two hundred and eighty patients (39.0%) had RI, in which 61 patients (8.5%) reached the level of moderate or severe RI. Patients with RI were more often female, elderly, hypertensive, and more patients had heart failure and stroke with higher killip class. Patients with RI were less likely to present with chest pain. The inhospital mortality (1.4% vs. 5.9% vs. 22.9%, $P < 0.001$), 6-year all-cause mortality (9.5% vs. 19.8% vs. 45.2%, $P < 0.001$) and 6-year cardiac mortality (2.9% vs. 12.2% vs. 23.8%, $P < 0.001$) were markedly increased in patients with RI. After adjusting for other confounding factors, classification of admission renal function was an independent predictor of inhospital mortality (Odd ratio, 1.966; 95% confidence interval [CI], 1.002-3.070, $P = 0.019$), 6-year all-cause mortality (relative risk [RR] = 1.501, 95% CI: 1.018-4.373, $P = 0.039$) and 6-year cardiac mortality ($RR = 1.663$, 95% CI: 1.122-4.617, $P = 0.042$).

Conclusions: RI is very common in STEMI patients. RI evaluated by eGFR is an important independent predictor of short-term and long-term outcome in patients with acute STEMI.

Key words: In-hospital Mortality; Long-term Mortality; Myocardial Infarction; Renal Insufficiency

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. The overall prevalence of CKD in China is 10.8%, or about 119.5 million adults.[1] Renal insufficiency (RI) has been reported to be associated with cardiovascular disease, acute coronary syndrome.[2-9] Most of these studies were retrospective. Little is known about the impact of RI on the long-term outcome of patients with acute ST-elevation myocardial infarction (STEMI) in China.

Clarifying long-term risk associated with factors such as RI in patients with acute MI (AMI) becomes increasingly important as survival after AMI improves.[10,11] Long-term prognostic information helps to stratify patients accurately, guide management in both outpatient and acute inpatient settings and quantify long-term benefits of potentially invasive interventions.[7] Thus, we did a 6-year multicenter prospective cohort study to evaluate the impact of admission

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RI on the mortality in patients with STEMI over time, especially for patients with mild RI, and the effect on mortality of renal function or nonrenal risk factors over time.

Methods

Study design and population
We performed a multicenter, observational, prospective-cohort study with 718 of 808 consecutive STEMI patients admitted to 19 hospitals between January 1, 2006 and December 31, 2006.

Patients meeting the following criteria were included in the study: (1) ST-segment elevation > 0.1 mV in ≥ 2 continuous precordial leads or adjacent limb leads, or a new left bundle branch block; (2) elevated serum cardiac biomarkers; and (3) admission within 24 hours of symptom onset. Patients were excluded because (1) there was no baseline estimation of glomerular filtration rate (eGFR) data ($n = 90$); (2) they had communication problems (serious hearing and cognitives); (3) they were transferred from outside Beijing; or (4) they refused to participate in the investigation and follow up.

The study protocol was approved by the human research Ethics Committee at the People's Hospital of Peking University and was consistent with the Declaration of Helsinki. The study was explained to each patient and their family members, and a written informed consent was obtained.

Definition
The modified abbreviated modification of diet in renal disease formula based on the Chinese CKD patients was used to calculate eGFR, based on creatinine level on the day of admission. eGFR (ml·min^{-1}·1.73 m^{-2}) was calculated as: $186 \times$ (serum creatinine level (mg/dl)$^{-1.154} \times$ (age [years])$^{-0.203} \times$ (0.742 if female) $\times 1.233$ (for Chinese patients). The study population was stratified into three groups according to eGFR: No RI (eGFR ≥90 ml·min^{-1}·1.73 m^{-2}, $n = 438$), mild RI (60 ml·min^{-1}·1.73 m^{-2} ≤ eGFR <90 ml·min^{-1}·1.73 m^{-2}, $n = 219$) or moderate RI (eGFR <60 ml·min^{-1}·1.73 m^{-2}, $n = 61$). In this population, eGFR in 5 patients' was <30 ml·min^{-1}·1.73 m^{-2} and we classified them to moderate or severe RI.

Data collection
Standardized data during hospitalization were analyzed, including demographic and clinical data, laboratory results, therapy method (reperfusion therapy), complications and outcome. Complications included recurrent MI, stroke, new emerging heart failure or aggravated heart failure, malignant arrhythmias and severe bleeding (intracranial hemorrhage or hemoglobin lower ≥5 g/dl or Hct lower ≥15%).

After patients discharged we collected information by telephone about some events such as deaths, major adverse cardiac events (cardiovascular deaths, non-fatal MI, non-fatal cerebral stroke), readmission for cardiogenic causes and for revascularization from April 1, 2012 to June 31, 2012.

Statistical analysis
Continuous variables with normal distributions were expressed as mean ± standard deviation. Three groups were compared using analysis of variance. Non continuous data with a skewed distribution were presented as median (with 25% and 75%) and tested by the Mann-Whitney U-test. Categorical variables were expressed as frequencies and percentages, and tested by Chi-square and Fish.

Multivariate logistic regression analysis was performed to identify independent predictors of in-hospital mortality. The following baseline clinical characteristics were considered in the multivariate procedure: Age, gender, history of prior MI, history of heart failure, history of stroke, history of hypertension, history of diabetes, history of hypercholesterolemia, smoking, Killip class, systolic blood pressure on admission, diastolic blood pressure on admission, heart rate on admission, anterior location of infarction, time of symptoms to hospital door time, peak creatine kinase-MB, and the classification of renal function .

Multivariate Cox regression analysis was performed to identify predictors of inhospital and 6-year long-term mortality. The relationship between RI and up to 6-year all-cause mortality and cardiac mortality after adjustments to the variables including age, gender, history of stroke, history of hypertension, history of diabetes, killip class and the classification of renal function. Kaplan-Meier analysis with log-rank tests was performed to compare survival and cardiac death-free survival of the three groups. All statistical tests were two-tailed. $P < 0.05$ was considered statistically significant. All analyses were performed using the statistical software for windows (Statistical Package for the Social Sciences (SPSS) 17.0 SPSS Chicago, USA).

Results

Baseline characteristics
Seven hundred and eighteen patients with STEMI were evaluated. There were 551 men and 167 women with a mean age of 61.0 ± 13.0 years. Two hundred and eighty patients (39%) had RI, in which 61 patients (8.5%) reached the level of moderate RI. Among these patients, 382 (53.2%) had a history of hypertension and 147 (20.5%) had a history of diabetes mellitus. Their baseline characteristics and biochemical parameters were shown in Table 1.

Renal insufficiency was associated with older age, female gender, and higher prevalence of hypertension, heart failure and previous stroke [Table 1]. On admission time, we found that a lower eGFR was associated with a higher killip class, lower blood pressure, and lower haemoglobin and less opportunity of primary percutaneous coronary intervention (PPCI).

Clinical outcomes
A total of 37 (5.2%) deaths occurred in the hospital. Mortality rate increased with renal impairment. Six (1.4%) in normal renal function, 13 (5.9%) in mild RI and 17 (22.9%) in moderate or severe RI in patients with STEMI. The combined end points of deaths and major clinical complications in the hospital (such as malignant arrhythmiasand heart failure) increased with renal impairment [Table 2].

Table 1: Baseline characteristics by eGFR group

Items	Group			P
	GFR ≥ 90 ml·min^{-1}·1.73 m^{-2} (n = 438) % (n)	60 ≤ eGFR < 90 ml·min^{-1}·1.73 m^{-2} (n = 219) % (n)	eGFR < 60 ml·min^{-1}·1.73 m^{-2} (n = 61) % (n)	
Age (years)	56.7 ± 11.7	65.7 ± 12.7	71.9 ± 13.1	<0.001
Female gender	16.9 (74)	29.2 (64)	48.3 (29)	<0.001
Hypertension	47.7 (209)	59.8 (131)	70.5 (43)	<0.001
Diabetes	18.7 (82)	21.5 (47)	29.5 (18)	0.157
Hyperlipidemia	18.0 (79)	24.3 (53)	24.6 (15)	0.106
Previous stroke	8.9 (39)	10.6 (23)	19.7 (12)	0.027
Previous HF	0 (0)	2.7 (6)	6.6 (4)	<0.001
Previous coronary heart disease	21.0 (92)	29.2 (64)	36.1 (22)	0.006
Previous PAD	0.9 (4)	3.2 (7)	1.6 (1)	0.099
Previous renal insufficiency	0.2 (1)	1.8 (4)	13.1 (5)	<0.001
Cigarette smoking	64.6 (283)	42.0 (92)	36.1 (22)	<0.001
Heart rate on admission (BPM)	75.6 ± 15.9	73.9 ± 17.5	78.4 ± 23.4	0.174
SBP on admission (mmHg)	126.7 ± 24.4	123.6 ± 29.5	113.1 ± 33.4	0.001
DBP on admission (mmHg)	78.5 ± 15.6	74.6 ± 18.3	74.6 ± 18.3	<0.001
Symptoms to hospital door time [min M (Q1, Q3)] (min)	135 (75, 300)	135 (70, 300)	110 (70, 210)	0.771
Chest pain	91 (398)	89.2 (195)	82.6 (50)	0.039
Anterior infarction	45.9 (201)	39.7 (87)	41.0 (25)	0.284
Killip class II-IV	34.7 (152)	37.0 (81)	65.5 (40)	<0.001
Peak CK [U/L M (Q1, Q3)]	1671 (662, 3000)	1478 (641, 3007)	1332 (563, 2660)	0.332
Hemoglobin (g/L)	142.3 ± 20.9	139.5 ± 18.2	140.4 ± 20.3	<0.001
Baseline creatinine (μmol/L)	76.1 ± 14.3	102.1 ± 14.6	168 ± 12.5	<0.001
Baseline calculated GFR	119.7 ± 25.6	77.7 ± 7.9	48.1 ± 12.1	<0.001
PCI	75.8 (332)	68.0 (149)	60.7 (37)	0.013
Thrombolytic therapy	17.1 (75)	19.2 (42)	9.8 (6)	0.231

eGFR: Estimation of glomerular filtration rate; GFR: Glomerular filtration rate; PAD: Peripheral arterial disease; HF: Heart failure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; CK: Creatine kinase; PCI: Percutaneous coronary intervention.

Table 2: Baseline characteristics by follow-up

Items	Lost (n = 231) % (n)	Follow-up (n = 450) % (n)	P
Age (years)	60.00 ± 12.43	60.75 ± 12.39	0.853
Gender male	78.3 (181)	77.8 (350)	0.871
Hypertension	50.4 (116)	52.7 (237)	0.551
Diabetes	19.9 (46)	19.8 (89)	0.974
Hyperlipidemia	19.4 (45)	20.7 (93)	0.779
Previous HF	1.3 (3)	1.1 (5)	0.978
Previous stroke	9.1 (21)	10.4 (47)	0.662
Cigarette smoking	60.6 (140)	54.2 (244)	0.094
Killip class II-IV	33.3 (77)	37.1 (167)	0.331
Anterior infarction	55.4 (128)	49.1 (221)	0.115
Symptoms to hospital door time (min M [Q1, Q3])	140 (79,300)	120 (70,285)	0.298
Thrombolytic therapy	14.2 (33)	15.3 (69)	0.702
Primary coronary intervention	64.9 (150)	66.4 (299)	0.700

HF: Heart failure.

Median follow-up time was 5.76 years. 231 patients (33.9%) were lost to follow-up. There were no difference between the patients followed up and the patients lost about the baseline characteristics including eGFR [Table 2]. Four hundred and fifty in 681 survived patients were followed throughout the study. Seventy one (15.8%) patients died in 6 years. The incidence of all-cause mortality (45.2% vs. 19.8% vs. 9.5%), cardiac mortality (23.8% vs. 12.2% vs. 2.9%) and major adverse cardiac events (42.9% vs. 22.1 vs. 22.7%) were higher in patients with RI than those with normal renal function [Table 3].

Baseline RI was associated with a statistically significant increase of in-hospital and 6-year mortality [Table 3]. After adjustment for other risk factors, the classification of renal function at baseline remained an independent predictor of in-hospital mortality (Odd ratio: 1.966, 95% confidence interval [CI]: 1.002-3.070, P = 0.019) [Table 4]; all-cause death (relative risk [RR]: 1.501, 95% CI: 1.018-4.373, P = 0.039) and cardiac death (RR: 1.663, 95% CI: 1.122-4.617, P = 0.042) during the follow-up period [Tables 4 and 5]. Patients with worse levels of RI had a significantly higher 6-year all-cause mortality rate and cardiac mortality rate [Figures 1 and 2].

DISCUSSION

The main finding of this study was that RI is very common in patients with STEMI. Nearly two-fifth of these patients had RI. The classification of renal function on admission was a strong independent risk factor for inhospital and

Table 3: Outcome by eGFR group % (*n*)

Items	GFR ≥ 90 ml·min⁻¹·1.73 m⁻²	60 ≤ GFR < 90 ml·min⁻¹·1.73 m⁻²	eGFR < 60 ml·min⁻¹·1.73 m⁻²	P	Total
	Group				**Total**
Hospital outcomes % (*n*)					
n	438	219	61		718
Death	1.4 (6)	5.9 (13)	22.9 (17)	<0.001	5.2 (37)
Recurrent myocardial infarction	1.1 (5)	2.7 (6)	3.3 (2)	0.204	1.8 (13)
Stroke	0.5 (2)	0.5 (1)	0 (0)	0.883	0.5 (3)
New emerging or aggravated HF	10.7 (47)	16.4 (36)	34.4 (21)	<0.001	14.5 (104)
Malignant arrhythmia	6.4 (28)	10.5 (23)	29.5 (18)	<0.001	9.6 (69)
Severe bleeding	1.6 (7)	3.2 (7)	4.9 (3)	0.085	2.4 (17)
MACE	18.0 (79)	27.4 (60)	63.9 (39)	<0.001	24.8 (178)
6 year outcome % (*n*)					
n	277	131	42		450
All-cause death	9.5 (26)	19.8 (26)	45.2 (19)	<0.001	15.8 (71)
Cardiac death	2.9 (8)	12.2 (16)	23.8 (10)	<0.001	7.6 (34)
Recurrent myocardial infarction	14.4 (40)	8.4 (11)	4.8 (2)	0.193	11.6 (53)
Stroke	5.4 (15)	1.5 (2)	14.2 (6)	0.017	5.1 (23)
Cardiac rehospitalization	20.9 (58)	16.8 (22)	26.2 (11)	0.346	20.2 (91)
PCI again	11.2 (31)	5.3 (7)	8.3 (1)	0.072	8.7 (39)
CABG	2.5 (7)	1.5 (2)	0	0.164	2.4 (9)
MACE	22.7 (63)	22.1 (29)	42.9 (18)	<0.001	24.2 (110)

eGFR: Estimation of glomerular filtration rate; GFR: Glomerular filtration rate; HF: Heart failure; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; MACE: Major adverse cardiac event.
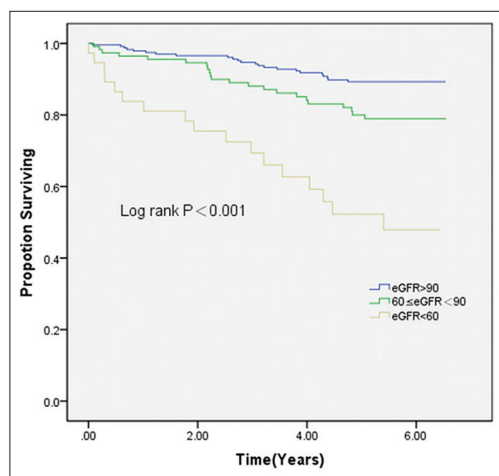

Figure 1: Kaplan–Meier survival curves during 6-year follow-up in patients with baseline eGFR ≥90 ml·min⁻¹·1.73 m⁻², 60 ≤eGFR <90 or eGFR <60 ml·min⁻¹·1.73 m⁻².
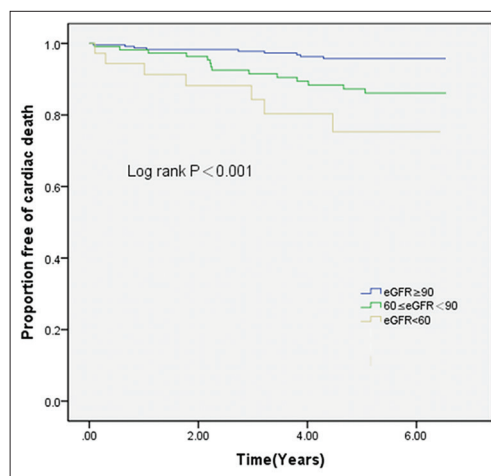

Figure 2: Kaplan–Meier curve of cardiac mortality during 6-year follow-up in patients with baseline eGFR ≥90 ml·min⁻¹·1.73 m⁻², 60 ≤eGFR <90 or eGFR <60 ml·min⁻¹·1.73 m⁻².

6-year mortality. Compared patients with admission normal function, the mortality increased by about 4-fold in-patinets and 3-fold in out-patients with moderate or severe RI; the mortality increased by 2-fold in-patinets and 1.6-fold in out-patients with mild RI. Kaplan Meier analysis clearly demonstrated the different survival of the three groups.

Numerous studies have demonstrated that impaired renal function is associated with short-term mortality and 2–8-fold increased risk of death compared to patients with normal renal function,[3-6] our study results were consistent with those findings. It is suspected that the results can reflect the real world. During past years few studies have addressed

the long-term mortality of patients with impaired renal function, in particular patients hospitalized with STEMI. In a secondary analysis of the Valsartan in AMI Trial, Anavekar *et al*.[4] found an increased risk of cardiovascular events and death in patients with AMI and heart failure or left ventricular dysfunction. Patients with an eGFR <81 ml were at the highest risk. However, follow-up in this study was only 2 years. A 6-year follow-up study[14] showed that only severely reduced renal function was an important and independent risk factor for mortality after AMI. The risk associated with a moderate reduction in renal function was explained by an association with other medical conditions.

Table 4: Multivariable logistic regression analysis of hospital mortality

Items	OR	95% CI	P
HTN	5.867	1.616 - 21.299	0.007
Previous DM	2.402	0.891 - 6.477	0.083
Previous stroke	3.053	1.044 - 8.931	0.042
Classification of renal function	1.966	1.002 - 3.070	0.019
Killip class	2.889	1.019 - 8.191	0.046
DBP on admission (mmHg)	0.941	0.910 - 0.974	<0.001

OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus; HTN:Hypertension; DBP: Diastolic blood pressure.

Table 5: Multivariable cox regression analysis of 6-year all-cause mortality and cardiac mortality

Items	RR	95% CI	P
6-year all-cause mortality			
Age	1.066	1.031 - 1.103	<0.001
Previous stroke	2.463	1.224 - 4.957	0.012
Killip class	2.226	1.185 - 4.182	0.013
Classification of renal function	1.501	1.018 - 4.373	0.039
6-year cardiac mortality			
Age	1.053	1.008 - 1.100	0.021
Previous stroke	3.045	1.139 - 8.137	0.026
Killip class	2.030	1.263 - 3.263	0.003
Classification of renal function	1.663	1.122 - 4.617	0.042

RR: Relative risk; CI: Confidence interval.

It should be emphasized that this study enrolled patients 20 years ago, when therapy of STEMI was significantly different from today. 11,873 cases of AMI were enrolled (about 30% of whom had STEMI) in a retrospective study and Smith concluded that baseline renal function was one of the most important predictors of mortality during 10 years follow-up, besides patient age.[6] There was a 10% increased risk for death associated with mild levels of renal impairment (Chemotherapy-related cognitive impairment [CrCI] <74 ml/min) and a doubling of the death rate associated with severe impairment (CrCI < 27 ml/min). This study was limited to elderly patients (age ≥ 65 years). Ours is the first study addressing the ultra-long-term mortality of patients hospitalized for STEMI in China. We confirmed that RI including mild RI on admission was a strong predictor of not only in-hospital mortality, but also for long-term mortality.

Similar to previous studies,[2-9,12,14] we found that patients with RI and STEMI were older and more likely to have a history of cardiovascular risk factors than patients with normal renal function. These patients often had a previous history of heart failure and stroke, a reflection of their more severe coronary disease and advanced stage of atherosclerotic disease. These patients had a higher incidence of cardiovascular events in the hospital, including malignant arrhythmias, new emerging heart failure and aggravated heart failure. RI has been reported to be associated with a higher mortality. This is thought to be related to the presence of left ventricular hypertrophy with chronic volume or pressure overload[15,16]

and electrolyte disorders caused by impaired renal function. Therefore, close surveillance is needed to reduce the cardiac workload and maintain water and electrolyte balance.

Primary percutaneous coronary intervention (PPCI) has become the first-line therapeutic option for patients with STEMI. PPCI limits the extent of infarction and decreases the risk of mortality[17] as showed in our study. PPCI was performed less frequently in our patients with worse levels of RI than in those with no RI [Table 1]. The underutilization of effective therapies might have contributed to their poor outcome. We also found that patients with RI more often presented with atypical symptoms before seeking medical care, similar to previous studies,[8,18,19] which is related to poor outcome too. But there is not obvious delays difference between three groups, all the patients lived in Beijing urban district and near to hospital may be the reason. Clinicians' fear of adverse events, such as bleeding, contrast-induced nephropathy or renal function deterioration, may be the other reason. Chinese guideline recommendations for the treatment of STEMI are similar for patients with RI and for the general population.[20] So clinicians should take more PPCI for patients with renal dysfunction with STEMI to improve their prognosis when they can be applied with an acceptable level of safety.

After adjusting for age, gender, and other risk factors, RI was still a strong independent predictor of in-hospital mortality and of 6-year mortality in patients with STEMI. Pathophysiology related to renal dysfunction, such as oxidative stress, pro-inflammatory and prothrombotic states (which can lead to endothelial dysfunction, accelerated atherosclerosis, blood coagulation and more thrombotic events) may be the cause of the poor prognosis of patients with STEMI.[4,5,21,22] It has been reported that hyperhomocysteinemia, proteinuria and anaemia are associated with RI in these patients, which may also contribute to their poor prognosis.[5,22]

This study had two limitations. The first is all of the patients were selected from secondary or tertiary medical centers in Beijing, where medical care is relatively good. This could result in a selection bias. The second is absence of renal function monitoring during hospitalization impeded an evaluation of the degree of change of renal function from admission and its impact on survival.

This study demonstrated that RI is very common in STEMI patients and admission RI was independently associated with a higher in-hospital and long-term mortality of patients with STEMI. Patients with STEMI and admission RI warrant close surveillance and intensive management in order to prevent recurrent cardiovascular events and decrease mortality.

ACKNOWLEDGMENTS

(Tianchang Li); General Hospital of Chinese People's Liberation Army (Hong Shen); Beijing Anzhen Hospital of the Capital Medical University (Hongbing Yan); Beijing Xuanwu Hospital of the Capital Medical University (Qi Hua); Beijing Fuwai Cardiovascular Hospital, Chinese Academy of Medical Sciences (Jun Zhu); Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (Quan Fang); General Hospital of Beijing Military Command of Chinese People's Liberation Army (Xian Wang); Peking University Shou Gang Hospital (Laijing Guo); Beijing No. 6 Hospital (Xiaoping Xiang); Beijing Chuiyangliu Hospital (Ruijie Li); Beijing Shijingshan Hospital (Mingsheng Wang); Beijing Chaoyang Hospital West Yard, Capital Medical University (Jianjun Zhang); Beijing Electric Power Hospital, North China Electric Power Company (Buxing Shen); Beijing Shunyi Hospital (Zhengyan Zhu); Beijing Hepingli Hospital (Lijing Zhang); Beijing Jiangong Hospital (Zechang Xu); Beijing Mentougou Hospital (Dezhao Wang); and Beijing Tongren Jingyuan Hospital (Xinquan Zhang).

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