SHORT REPORT

Risk factors for elderly acute decompensated heart failure patients with diabetic nephropathy: A retrospective study

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Abstract

Risk factors that contribute to the development of heart failure include chronic kidney disease and diabetes. Elderly patients with diabetic nephropathy are more likely to develop heart failure. We analysed laboratory data and clinical characteristics of elderly patients with diabetic nephropathy to explore the risk factors for therapeutic effect of acute decompensated heart failure (ADHF). One hundred and five elderly patients with diabetic nephropathy, admitted in the Nephrology Ward of Baoding No1 Central Hospital Baoding, China, between June 2018 and June 2020, were enrolled in this study. They were classified as biochemically unaltered group (21 cases) and biochemically recovering group (84 cases). The clinical data, laboratory examination, therapy, and outcome of the participants were collected for analysis retrospectively. Low-density lipoprotein (LDL), C-reactive protein (CRP) and 24-hour urine protein are independent risk factors for the therapeutic efficacy of ADHF in elderly patients with diabetic nephropathy.

Keywords: Diabetic Nephropathy, Chronic kidney disease, Risk factors, Biomarkers.

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Introduction

Diabetes Mellitus is a metabolic disorder with many complications, of which microvascular complications are the main cause of death. One of these is Diabetic nephropathy (DN), an important microvascular complication, occurring in 20-40% of patients with diabetes mellitus (DM).[1-3] In developed countries, diabetic nephropathy (DN) is the main cause of end-stage renal disease (ESRD).[4,5] The progression of the course of DN represents a complex mechanism including haemodynamics, activation of neuro-humoral, and inflammatory factors which cause multiple complications. Complications include increased acute kidney injury, kidney-disease progression, and cardiovascular mortality.[6] Of these, cardiovascular system damage is the most common complication, while cardiovascular disease (CVD), especially heart failure, has replaced infection as the primary life-threatening problem.[7] Most patients with heart failure are elderly with diabetic nephropathy, and the prevalence increases with age. The transition from compensatory cardiac dysfunction to the acute symptom phase is defined as acute decompensated heart failure (ADHF). Once DN patients developed ADHF, the fatality rate and disability rate increased significantly.[8,9] Therefore, it is important to establish relevant risk factors for patients with DN and ADHF. For patients who survive the acute phase, the risk of re-compensation or death due to cardiac function is still high, more stringent control of indications for drugs or invasive treatment and closer follow-up observation are required.

Here, we present the clinical manifestations and laboratory examinations of elderly stage 4 diabetic nephropathy patients with ADHF; our aim was to find risk factors and establish models for the prediction.

Methods and Results

The study included elderly patients with diabetic nephropathy from the Nephrology Ward in Baoding No. 1 Central Hospital Baoding, China, between June 2018 and June 2020. This study was approved by the ethics committee of Baoding No. 1 Central Hospital to protect human subjects. The methods employed followed the relevant protocols.

The clinical data of the patients during their stay in the Nephrology Ward was collected by medical researchers. The duration from hospital admission to discharge were recorded. Anthropometric characteristics, including height, weight, waist circumference, and blood pressure, were measured. Hypertension was defined as patients taking anti-hypertensive medication or whose blood pressures was greater than 140/90 mmHg. The different treatments employed during hospitalisation were also recorded.

Inclusion criteria were patients with type 2 DM and evidence of diabetic nephropathy, based on Chinese Type 2 Diabetes Mellitus (T2DM) Prevention and Treatment Guidelines (2017 edition),[10] admitted with 24-hour urine protein>0.5g and eGFR>90 ml/min/1.73m^2. Secondly acute decompensated heart failure defined as, a) patients with a history of heart failure (HF) for > 5 years and b)

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Table-1: Demographic characteristics of elderly patients with diabetic nephropathy.

Study of population	Biochemically recovering group (n=84)	Biochemically unaltered group (n=21)	χ^2/t/Z	P value
Gender				
Male (n, %)	41 (47.08)	19 (45.81)	0.032	0.638
Female				
Age, median (IQR), y	67 (65-79)	68 (65-78)	-0.193	0.569
Days in hospital (d)	10 (8-11)	11 (9-13)	-1.837	0.046*
BMI(kg/m^2)	26.32 (±3.14)	26.72 (±2.29)	0.635	0.427
Systolic blood pressure (mmHg)	152 (138-160)	159 (132-166)	-1.245	0.167
Diastolic blood pressure (mmHg)	81 (75-90)	84 (74-93)	-0.859	0.363
Comorbidities (n, %)				
Hypertension	66 (83.52)	17 (87.45)	0.635	0.002**
Coronary Heart Disease	43 (52.82)	12 (52.89?	0.320	0.736
Dyslipidaemia	20 (22.42)	8 (41.67)	6.728	0.323
Atrial fibrillation	30 (34.85)	9 (40.15)	0.241	0.607
Personal history (n, %)				
Smoking	51 (62.56)	12 (58.02)	0.786	0.450
Drinking	23 (26.68)	7 (30.98)	0.563	0.381
Treatment in hospital (n, %)				
Loop diuretics (furosemide, iv, 20mg*2/day)	70 (82.95)	18 (88.96)	1.598	0.301
β-blockers (metoprolol tartrate, 12.5mg*2/day)	58 (68.89)	16 (75.66)	1.509	0.293
Digitalis	36 (42.89)	9 (41.98)	1.109	0.301
(Cedilanid, iv, 0.2mg*1/day)				
Recombinant human brain natriuretic peptide (iv,0.5mg*1/day)	28 (32.97)	4 (20.01)	5.985	0.023*
Sodium nitroprusside (iv,25mg*1/day)	40 (48.01)	10 (46.98)	0.496	0.394
Nitroglycerine (iv, 20mg*1/day)	31 (36.48)	8 (39.49)	0.183	0.596

Table-2: Laboratory findings of elderly patients with diabetic nephropathy.

Laboratory Tests	Reference values	biochemically recovering group (N=84)	biochemically unaltered group (N=21)	χ^2/t/Z	P value
Hb(g/L)	115-150	97.85(83.25-112.38)	97.65(81.45-110.15)	-0.005	0.856
WBC (×10^9/mL)	3.5-9.5	7.93(6.32-10.15)	8.10(6.43-10.20)	-1.637	0.068
LDL (mmol/L)	1.4-3.7	2.36(1.89-3.12)	3.18(2.58-3.49)	-4.120	0.002**
24h-Upro(g)	0-0.15	2.13(1.50-2.85)	5.08(2.58-7.29)	-1.678	0.001**
HbAlc(%)	4.0-6.0	7.52(6.78-7.86)	7.61(6.98-8.19)	6.722	0.036*
CRP (mg/L)	0.0-8.0	6.69(4.25-8.96)	14.34(10.63-22.56)	-3.005	0.002**
Blood calcium (mmol/L)	2.11-2.52	1.62(1.43-1.81)	1.65(1.41-1.80)	-7.410	0.430
PTH (pg/mL)	15-75	151.21(92.75-196.38)	149.66(94.37-202.46)	-1.765	0.735
NT-proBNP(pg/mL)	<125	3232.8(2656.84-3802.26)	5126.2(4762.62-5453.83)	-6.325	<0.001**
Echocardiographic indication					
LVESD (mm)	20-40	35.00±6.52	36.00±6.32	0.457	0.626
LVEDD (mm)	35-55	48.00±5.34	50.00±4.99	0.542	0.635
LVEF(%)	55-80	58.00±3.65	56.00±5.39	1.196	0.795

Abbreviations: WBC-White blood cells, PLT-Platelets, HB-Haemoglobin, LDL-low-density lipoprotein, HbA1c- HaemoglobinA1c, CRP-C-reactive protein.

recent acute attack of heart failure confirmed according to the diagnostic criteria for heart failure recommended by the Chinese Heart Failure Diagnosis and Treatment Guidelines 2018,[11] and in line with the New York College of Cardiology (NYHA) heart function classification of grade IV.[12] All the patients were diagnosed as left heart failure (right heart and total heart failure by echocardiography).

Excluded were patients undergoing Renal replacement therapy or diagnosed with acute myocardial infarction, congenital heart disease or heart valve replacement surgery, acute coronary syndrome or cardiogenic shock, pulmonary embolism, systemic infectious diseases, severe liver or pancreatic disease or malignant tumours. Patients with acute kidney injury, myocarditis or pericarditis, and acute stroke were also excluded.

The selected patients were divided into two groups — biochemically unaltered group and biochemically recovering group — based on whether the decrease of N-

Table-3: Results of multiple logistic regression analysis.

	B	SD	P	OR	95% CI
Abnormal blood pressure	-0.175	0.218	0.625	0.786	0.496-1.384
LDL	-0.332	0.160	0.018*	0.621	0.468-0.866
CRP	-0.168	0.045	0.002**	0.756	0.831-0.960
24 h-Upro (g)	-0.324	0.302	0.001**	0.702	0.750-1.120
Recombinant Human Brain Natriuretic Peptide	0.115	0.050	0.465	1.095	1.000-1.198

Abbreviation: B-regression coefficient; SD-standard deviation; P-P-Value; OR-odds ratio; CI, confidence intervals;
"*" and "**" represent "P <0.05"and "p<0.01," respectively.

Table-4: AUC of the laboratory findings.

Markers	AUC
CRP	0.922
24 h-Upro	0.894
LDL	0.944

AUC- Area under the curve. CRP- C-Reactive Protein. LDL- Low Density Lipoprotein.

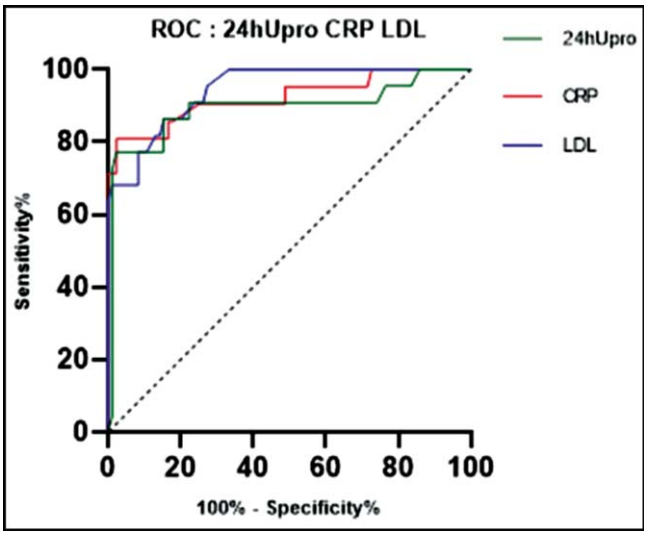

Figure-1: ROC curve.

terminal pro brain natriuretic peptide (NT-proBNP) on the day of discharge from the day of admission was less than 30%, according to 2018 guidelines for the diagnosis and treatment of heart failure in China and 2013 ACCF/AHA guideline for the management of heart failure.[11,13]

Median (interquartile range [IQR]), or number (%) was used to analyse the descriptive statistics of variables. Some data was missing, so the sample size varied. The comparison of categorical variables between biochemically unaltered and biochemically recovering groups were carried out using χ^2 test or Fisher's exact test. The clinical characteristics of the patients were assessed using univariate analysis, and the univariate differences was analysed with binary logistic regression. P value less than .05 was set as statistically significant. SPSS, version 25.0 (IBM SPSS) was used to perform statistical procedures.

This study included 105 patients (Table-1). The median age for biochemically recovering group was 67 years (IQR 65-79) and for biochemically unaltered group it was 68 years (IQR 65-78). Many participants showed complications, such as hypertension (66 [83.52%] for the biochemically recovering group and 17 [87.45%] for the biochemically unaltered group), coronary heart disease (43 [52.82%] for the biochemically recovering group and 12 [52.89%] for the biochemically unaltered group), dyslipidaemia (20 [22.42%] for the biochemically recovering group and 8 [41.67%] for the biochemically unaltered group), atrial fibrillation (30 [34.85%] for the biochemically recovering group and 9 [40.15%] for the biochemically unaltered group). Most patients, 70 [82.95%] for the biochemically recovering group and 18 [88.96%] for the biochemically unaltered group) needed Loop diuretics. β-blockers were required by 58 [68.89 %] for the biochemically recovering group and 16 [75.66%] for the biochemically unaltered group).

The laboratory results are shown in Table-2. The inflammatory related index C-reactive protein (CRP) increased in the biochemically unaltered group (14.34, [10.63-22.56]), while in the biochemically recovering group (6.69, [4.25-8.96]) it remained at the normal level (p< 0.002). The 24 h-Upro of the biochemically unaltered group (5.08, [2.58-7.29]) was more than two times higher than the biochemically recovering group (2.13, [1.50-2.85]) (p< 0.001). The LDL of the biochemically unaltered group (3.18, [2.58-3.49]) was also higher than the biochemically recovering group (2.36, [1.89-3.12]) (p< 0.002).

Prognostic evaluation: By collecting the data of all the effective cases and biochemically unaltered cases in our hospital till June 2020, we analysed the differences to assess the risk factors for predicting the disease outcome (Table-3). Compared with biochemically unaltered cases, the potential risk factors were CRP, LDL, 24 h-Upro and abnormal blood pressure. The ROC curve was used to compare various potential indicators (Figure-1), CRP, 24 h-Upro showed better performance than other indicators such as LDL (Table-3).

Conclusion

In this study, several factors including CRP, LDL, 24 h-Upro and abnormal blood pressure were noted to be associated with the outcome.

C-reactive protein (CRP) refers to proteins in blood plasma that rise sharply in response to inflammation, which is a key factor in the innate immune process and a valuable predictor and risk factor for cardiovascular diseases. It

exhibits many biological activities such as immune defence to infection by interacting with complement Clq and FcTR. Serum levels of inflammatory markers including CRP, fibrinogen, IL-6 increased in almost 30-50% of CKD patients, which could cause cardiac hypertrophy and contractile dysfunction, indicating the monitoring value of CRP in heart failure patients.[14-16]

Low-density lipoprotein (LDL) is a kind of lipoprotein. Accumulation of small dense atherogenic LDL results in increased AT1 receptor, Ang-II, and activation of the renin-angiotensin system, which will stimulate NAD(P)H oxidase, xanthine oxidase, etc., leading to production of superoxide.[17,18] Elevated superoxide relates to endothelial dysfunction, decreased bioavailability of nitric oxide, hypertension, and vascular remodelling. In our study, this accumulation of LDL is also consistent with Kaysen' research.[18]

We achieved excellent differentiation of biochemically unaltered and biochemically recovering groups with AUC (0.922) by using CRP (Table-4), indicating that inflammation hinders the recovery of patients. CRP, LDL, and urine protein levels in the biochemically unaltered group were significantly higher than those in the biochemically recovering group, suggesting that lowering CRP, LDL, and urine protein levels may significantly improve heart function in elderly patients with heart failure.

This study has some limitations. First, this is a single centre study with small sample size. These biomarkers need to be validated by other cohorts. Second, this study lacks some data including IL-6, D-dimer, etc.

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Disclaimer: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was carried out in accordance with the recommendations of the institutional committee for the Protection of Human Subjects from Baoding No1 Central Hospital. All methods were performed in accordance with the relevant guidelines and regulations.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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