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**Optimal cutoffs of NT-proBNP for risk prediction in new-onset heart failure in chronic kidney disease across eGFR category**

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**Objectives :** The predictive utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for new-onset heart failure (HF) in chronic kidney disease (CKD) patients, especially in advanced CKD, remains confused. We aimed to describe the reference value of NT-proBNP, investigate the prognostic ability of NT-proBNP and identify the optimal cutoffs of NT-proBNP for risk prediction in new-onset HF in CKD patients without HF history across a wide distribution of estimated glomerular filtration rate (eGFR) category.

**Methods :** This retrospective cohort study enrolled CKD patients without previous HF history who had at least one record of NT-proBNP from China Renal Data System database. Included participants were divided into G1-2, G3a, G3b, G4 and G5 according to eGFR. We described the reference value of NT-proBNP in CKD patients without HF with different CKD stages. A follow-up cohort was created to assess the association of NT-proBNP and new-onset HF by Cox regression model and restricted cubic spline. Optimal cutoffs of NT-proBNP for the risk prediction in new-onset HF were identified across eGFR category.

**Results :** Among 36663 patients with CKD without HF, the reference value of NT-proBNP elevated with eGFR decreased. Follow-up cohort included 18261 eligible participants. NT-proBNP was positively associated with the risk of new-onset HF and improved the predictive ability of clinical variables to evaluate the risk of HF in different CKD stages. The non-linear relationship between NT-proBNP and new-onset HF shaped reversed L. Furthermore, the optimal cutoffs of NT-proBNP to predict new-onset HF increased as eGFR reduced in CKD (661, 834, 998, 1407, 5079 pg/mL, for G1-5, respectively), with a moderate discrimination in new-onset HF prediction within 6 month.

**Conclusions :** In CKD without HF, NT-proBNP maintained its prognostic value for the risk prediction in new-onset HF in different CKD stages. As the eGFR declined, the eGFR-specific reference values and optimal cutoffs of NT-proBNP to predict new-onset HF elevated.

Table 1.png

**Table 1.** The 95<sup>th</sup> and 99<sup>th</sup> reference value of NT- proBNP among CKD patients by eGFR category.

eGFR category	N	95 <sup>th</sup> NT- proBNP (pg/mL)	99 <sup>th</sup> NT- proBNP (pg/mL)
G1-5	36663	1520 (1488, 1552)	2239 (2181, 2296)
G1-2	17144	492 (479, 506)	662 (639, 685)
G3a	6057	1126 (1078, 1175)	1426 (1351, 1501)
G3b	4895	1821 (1731, 1909)	2466 (2318, 2612)
G4	4134	3120 (2957, 3281)	3861 (3643, 4081)
G5	4433	7153 (6843, 7461)	6974 (6677, 7271)

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 1.png

**Table 2.** Additional prognostic value and optimal cutoff of NT-proBNP for prediction in new-onset heart failure in CKD patients across eGFR category.

Groups	NRI (95% CI)	IDI (95% CI)	Cutoff value (pg/mL)	6-month AUC (95% CI)
G1-5	40.1 (34.8, 44.1)	1.7 (1.6, 1.8)	-	-
G1-2	34.7 (28.1, 41.5)	1.4 (1.2, 1.7)	661	72.1% (68.7%, 75.5%)
G3a	38.7 (29.8, 50.2)	2.1 (1.8, 2.4)	834	66.2% (61.7%, 70.8%)
G3b	46.2 (32.7, 57.1)	2.0 (1.6, 2.4)	998	67.1% (62.6%, 71.6%)
G4	43.5 (27.5, 57.1)	1.6 (1.3, 1.9)	1407	71.5% (66.9%, 76.1%)
G5	47.2 (0.36, 59.7)	1.3 (0.9, 1.6)	5079	68.4% (63.2%, 73.5%)

The additional predictive value of NT-proBNP was evaluated by net reclassification index and integrated discrimination improvement of adding NT-proBNP to clinical model. Clinical model consist of variables which were associated with heart failure in univariable cox analyses across eGFR categories; For CKD stages 1-2, the clinical model included age, SBP, DM, LDL, CCI, UA, HBG, diuretic, CVD history, statin and diabetes agent usage; for CKD stage 3a, the clinical model included age, BMI, CCI, LDL, UA, Alb, HBG, CVD history and diuretic usage; for CKD stage 3b, the clinical model included age, SBP, LDL, CCI and UA; for CKD stage 4, the clinical model included age, SBP, CCI, Alb, HBG, CVD history and diuretic usage; for CKD stage 5, the clinical model included age, SBP, CCI, CVD and PVD history.

Abbreviations: NRI, net reclassification index; IDI, integrated discrimination improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DM, diabetes mellitus; LDL, low-density lipoprotein cholesterol; CCI, Charlson Comorbidity Index; UA, uric acid; HBG, hemoglobin; CVD, cardiovascular disease; BMI, body mass index; Alb, albumin; PVD, peripheral vascular disease.