Original Article

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Heart rate is associated with mortality in patients undergoing continuous renal replacement therapy

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Background: Heart rate (HR) is an essential vital sign based on the finding that HR beyond its normal range is associated with several conditions or diseases, including high mortality in several clinical settings. Nevertheless, the clinical implications of HR remain unresolved in patients undergoing continuous renal replacement therapy (CRRT).
Methods: This retrospective cohort study included 828 patients who underwent CRRT due to acute kidney injury between 2010 and 2014. HR and other baseline parameters at the time of CRRT initiation were retrieved. The odds ratio (OR) of 30-day mortality was calculated using a multivariate logistic model.
Results: CRRT significantly lowered the HR of patients such that the pre- and post-CRRT HRs (average 6 hours) were 107 beats/min and 103 beats/min, respectively ($P < 0.001$). When we explored the relationship with 30-day mortality, only HR at the time of CRRT initiation, but not pre- or post-CRRT HR, had a significant relationship with mortality outcome. Based on this result, we divided patients into quartiles of HR at the time of CRRT initiation. Mortality OR in the 4th quartile HR group was 2.6 (1.78–3.92) compared with the 1st quartile HR group. This relationship remained consistent despite adjusting for 28 baseline covariates: OR, 1.7 (1.09–2.76); $P = 0.020$. However, HR was not associated with the weaning rate from CRRT.
Conclusion: High HR at the time of CRRT initiation is subsequently related with high mortality. These results can be a basis for a future predictive model of CRRT-related mortality.

Keywords: Acute kidney injury, Continuous renal replacement therapy, Heart rate, Mortality

Introduction

Continuous renal replacement therapy (CRRT) controls biochemical imbalance and uremic toxicity in patients with both acute kidney injury (AKI) and hemodynamic instability, which frequently occurs in the intensive care unit. Because of the high incidence of AKI in the intensive care unit, the use of CRRT has increased over the past few years [1]. However, despite the wide use of CRRT, guidelines for the initiation of or weaning from CRRT have not been established. In this respect, certain clinical uses of CRRT might not be restricted even in the risk of overwhelming disadvantages compared with less survival benefit.

Several reports in an intensive care unit have failed to demonstrate the superiority of CRRT compared with conventional intermittent hemodialysis in terms of survival benefit [2,3]. Because the patient subset requiring CRRT already is associated with high mortality risk [4,5], CRRT could not confer visible survival benefit in these studies.

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Nevertheless, refraining from obligatory CRRT initiation in all patients with AKI and hemodynamic instability is recommended because of the lack of guidelines and evidence.

CRRT can result in the hemodynamic instability of patients due to intravascular volume depletion and intercompartmental shifts [6]. This disadvantage of CRRT is aggravated by large volume depletion and impaired myocardial function of patients, particularly at the time of connection or early period. The implication of hemodynamic instability represents high patient mortality [4,7,8]. Although this issue has been significantly considered in clinical practice, the optimal values of vital signs for CRRT initiation remain unresolved.

Higher heart rate (HR) is associated with cardiovascular morbidity and mortality across several diseases [9]. This parameter has the advantage of inexpensive and simple measurement, but straightforward concern for HR might be less received in clinical practice compared with blood pressure because certain studies showed a week relationship between HR and mortality [10,11]. Nevertheless, HR is an essential requisite to monitor vital status, and its impact affects the relationship with non-cardiovascular mortality [12]. Herein, we firstly addressed the relationship between HR and overall mortality in a cohort undergoing CRRT due to severe AKI.

Methods

Participants and data collection

Data on patients starting CRRT were obtained retrospectively from a database of a tertiary referral center (Seoul National University Hospital). The inclusion criteria were as follows; adult patients (age, ≥ 18 years) admitted to the intensive care unit and need for CRRT due to severe AKI. Accordingly, 890 patients were enrolled between June 2010 and September 2014. We excluded patients who were previously diagnosed with end-stage renal disease or who were on dialysis before enrollment (n = 61). If the patients underwent CRRT more than once (n = 1), only the first experience was counted as a single case. Consequently, data from 828 patients were analyzed for the present study. The study protocol complied with the Declaration of Helsinki and received full approval from the institutional review board of Seoul National University Hospital (No. H-1610-070-799).

Clinical parameters of patient age; sex; HR; systolic and diastolic blood pressures; weight; cause of AKI; dialysis dose; blood flow rate; dialysate and replacement settings; need for mechanical ventilation; use of vasoactive drugs, anti-coagulants, beta blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; and underlying chronic kidney disease, diabetes mellitus, or atrial fibrillation were recorded at the start of CRRT. The HRs at the time of initiating CRRT, before, and after CRRT (average values during 6 hours) were measured by an automatic monitoring device in the intensive care unit. The mean arterial pressure was calculated as [systolic + (2 × diastolic)]/3. The causes of AKI were divided into sepsis, surgery, nephrotoxins, and others. The Acute Physiology and Chronic Health Evaluation (APACHE) II [13] and Sepsis-related Organ Failure Assessment (SOFA) [14] scores were calculated to quantitatively assess each patient's status. Blood parameters of hemoglobin, blood urea nitrogen, creatinine, and albumin levels were measured. Volume balance during the first 24 hours of CRRT was recorded as input minus output. The target dose during CRRT initiation was determined based on each patient's state. No data for any of the variables was missing. All patients were followed up until CRRT was discontinued or December 2016, except for death-censored cases. The primary outcome was all-cause mortality within 30 days. The secondary outcome was weaning from CRRT within 30 days.

Statistical analysis

Data are presented as the mean ± standard deviation for the continuous variables and as the proportion for the categorical variables. The variables with non-normal distributions are expressed as the median (interquartile ranges) based on variable distributions using histograms. The chi-square test was used to compare categorical variables. The comparisons between normally and non-normally distributed continuous variables were performed using the Student's *t*-test and Mann-Whitney *U* test, respectively. Cumulative survival curves were drawn using the Kaplan–Meier method. To compare the curves between the groups, the log-rank test was initially applied. The logistic regression model was used with or without adjustments for all covariates in order to calculate the odds ratios (ORs) of the outcome. A restricted cubic spline analysis was applied to account for the nonlinear

relationship between HR and mortality risk. A value of $P < 0.05$ was considered significant. All analyses and calculations were performed using the IBM SPSS Statistics software (version 21.0; IBM Co., Armonk, NY, USA) and STATA software (version 12.0; Stata Co. LP., College Station, TX, USA).

Results

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. Of the patients, 36.7% and 35.1% had sepsis and underlying chronic kidney disease, respectively. When

Table 1. Baseline characteristics of the patients at the time of starting continuous renal replacement therapy

Characteristic	Total (n = 828)	30-day mortality		
		No death (n = 419)	Death (n = 409)	*P* value
Age (yr)	63.1 ± 15.1	62.6 ± 15.8	63.7 ± 14.4	0.280
Male sex (%)	60.3	57.5	63.1	0.102
Heart rate (beat/min)	106.0 ± 25.4	101.5 ± 24.6	110.5 ± 25.3	< 0.001
Systolic blood pressure (mmHg)	111 ± 25	114 ± 26	109 ± 26	0.018
Diastolic blood pressure (mmHg)	65 ± 15	66 ± 16	64 ± 16	0.083
Mean arterial pressure (mmHg)	80 ± 18	82 ± 17	79 ± 18	0.028
Body weight (kg)	63.3 ± 12.5	63.3 ± 12.4	63.3 ± 12.7	0.961
Cause of acute kidney injury (%)				< 0.001
Sepsis	36.7	30.1	43.5	
Surgery	9.3	16.0	2.4	
Nephrotoxin	8.5	8.8	8.1	
Other	45.5	45.1	46.0	
Dialysis dose (mL/kg/hr)	43.3 ± 15.7	43.2 ± 15.6	43.3 ± 15.7	0.948
Blood flow rate (mL/min)	109 ± 22	109 ± 23	108 ± 22	0.232
Dialysate flow (mL/hr)	1,511 ± 653	1,495 ± 648	1,527 ± 658	0.481
Replacement flow (mL/hr)	1,491 ± 657	1,476 ± 656	1,506 ± 659	0.524
Mechanical ventilation (%)	26.7	33.4	19.8	< 0.001
Use of vasoactive drugs (%)	75.5	70.2	80.9	< 0.001
Use of anti-coagulant drugs (%)	40.9	43.9	37.9	0.078
Use of beta blockers (%)	4.3	4.8	3.9	0.543
Use of calcium channel blockers (%)	6.9	4.8	9.0	0.015
Use of ACEi/ARB (%)	2.3	2.6	2.0	0.520
Chronic kidney disease (%)	35.1	40.3	29.8	0.002
Diabetes mellitus (%)	22.5	23.6	21.3	0.417
Atrial fibrillation (%)	4.2	5.0	3.4	0.256
Blood findings				
Hemoglobin (g/dL)	9.7 ± 2.1	9.9 ± 2.1	9.6 ± 2.2	0.060
Blood urea nitrogen (mg/dL)	56.0 ± 32.0	52.5 ± 29.4	59.5 ± 34.1	0.002
Creatinine (mg/dL)	3.0 ± 1.8	3.0 ± 1.8	2.9 ± 1.9	0.436
Albumin (g/dL)	2.7 ± 0.6	2.8 ± 0.6	2.7 ± 0.5	0.001
Volume balance (mL/day)	830 (−66 to 2,369)	402 (−287 to 1,641)	1,282 (262 to 3,027)	< 0.001
APACHE II score	30.5 ± 9.1	27.9 ± 8.0	33.1 ± 9.5	< 0.001
SOFA score	12.7 ± 3.4	11.7 ± 3.3	13.7 ± 3.3	< 0.001

Data are presented as mean ± standard deviation, percent only, or median (interquartile range).

Comparisons were evaluated using the chi-squared test for categorical variables, the Student *t*-test for normally distributed continuous variables, and the Mann-Whitney *U* test for non-normally distributed continuous variables.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment.

we compared characteristics between patients who survived or died within 30 days of CRRT, a difference in HR was identified, such that those who died had higher HRs than those who survived. Furthermore, the patients who died had higher APACHE II and SOFA scores than those who survived, which indicated that illness severity was prominent in patients who died.

Relationship between heart rate and mortality

CRRT lowered the HRs of patients such that the pre- and post-CRRT HRs (i.e., average values during 6 hours) were 107 beats/min and 103 beats/min, respectively ($P < 0.001$). Within 30 days of CRRT, 409 patients (49.4%) died. We addressed the independent relationship between HR values and 30-day mortality. When we divided the patients by quartiles of HR, only HR at the time of CRRT initiation, not the average values of pre- and post-CRRT HRs, had a significant relationship with mortality outcome. Therefore, we used the HR values at the time of CRRT in all subsequent analyses. The overall survival curves are shown in Fig. 1. The group with high HRs showed higher mortality rates than the counterpart groups ($P < 0.001$ by the log rank test). When we calculated the OR of 30-day mortality (Table 2), the group with high HRs had a higher OR than the group with low HRs, irrespective of other covariates. As a sensitivity analysis, we additionally adjusted the volume balances 24 hours before the initiation of CRRT and 48 and 72 hours after initiation in the multivariate model (n = 596). The adjusted OR of the 4th quartile group was 2.22 (1.246–3.948) compared with the 1st quartile group ($P = 0.007$).

The adjusted OR was 1.01 (1.002–1.015) when HR was included as a continuous variable ($P = 0.012$). This suggests that an increase in 1 beat/min of HR was associated with a 1% increase in mortality rate. Subsequently, a restricted cubic spline analysis was used to explore the possible non-linear relationship between HR and predictability of 30-day mortality (Fig. 2). As a result, the re-

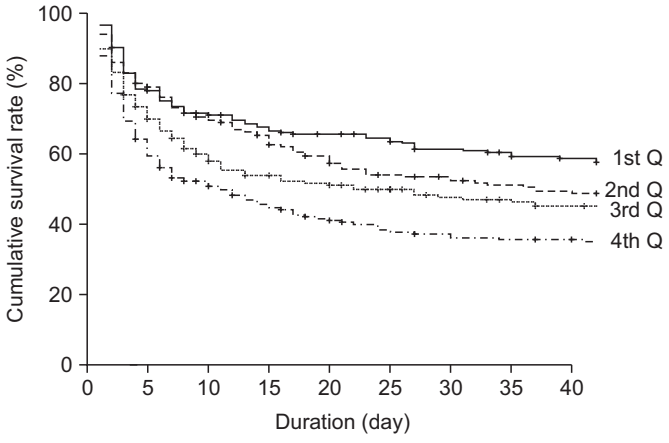

Figure 1. Kaplan-Meier survival curves based on heart rate. The patients were divided into quartiles (Q) based on the heart rate. CRRT, continuous renal replacement therapy.

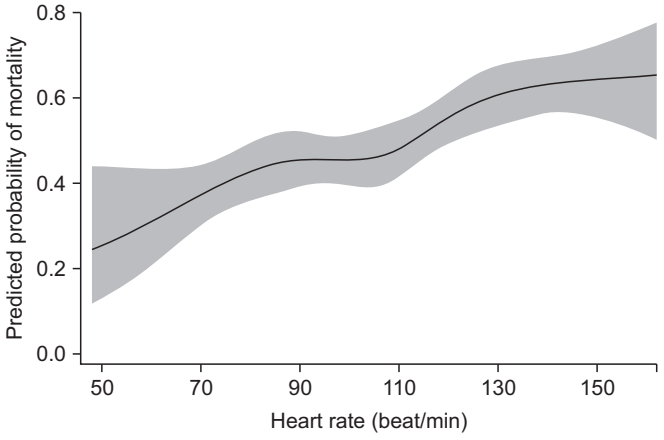

Figure 2. Exploring the possible nonlinear relationship between heart rate and probability of 30-day mortality. Fitted line and 95% confidence intervals are presented with the solid line and shaded area, respectively.

Table 2. Odds ratios for 30-day mortality according to the heart rate levels

Heart rate group	Range (beat/min)	Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
1st quartile	48–86	1 (Reference)		1 (Reference)	
2nd quartile	87–104	1.40 (0.94–2.08)	0.094	1.28 (0.83–1.99)	0.267
3rd quartile	105–123	1.68 (1.13–2.48)	0.010	1.38 (0.88–2.16)	0.156
4th quartile	124–186	2.64 (1.78–3.92)	<0.001	1.77 (1.11–2.81)	0.016

Model 1, unadjusted; Model 2, adjusted for all covariates shown in Table 1.
CI, confidence interval; OR, odds ratio.

Table 3. Weaning from continuous renal replacement therapy according to the heart rate levels

Heart rate group	Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1st quartile	1 (Reference)		1 (Reference)	
2nd quartile	0.87 (0.57–1.34)	0.525	1.05 (0.65–1.69)	0.835
3rd quartile	1.06 (0.70–1.60)	0.801	1.34 (0.83–2.16)	0.226
4th quartile	0.65 (0.42–1.00)	0.052	0.88 (0.53–1.48)	0.639

Model 1, unadjusted; Model 2, adjusted for all covariates shown in Table 1.
CI, confidence interval; OR, odds ratio.

lationship between HR and mortality seemed to be linear (not non-linear) in the CRRT subset.

Relationship with weaning from CRRT

We analyzed weaning from CRRT as a secondary outcome. No significant relationship between HR and weaning rate was shown in the analysis (Table 3). Subsequently, we analyzed only the patients who were alive at discharge because mortality could affect the weaning protocol of each patient (n = 419). Nevertheless, the following unadjusted and adjusted ORs of weaning in the 4th quartile group were not significant compared with the 1st quartile group: unadjusted OR, 1.43 (0.819–2.512); adjusted OR, 1.20 (0.619–2.326) (all $P > 0.05$).

Discussion

CRRT is a critical option to treat severe AKI cases, but the guidelines for initiating and weaning are insufficient, and no mortality-predicting models exist because of the lack of clinical data. The present study focused on HR, one of the widely used vital signs in cardiovascular and non-cardiovascular patients. As a result, high HR at the time of CRRT initiation was associated with subsequent high mortality. This result has clinical implications because no monitoring strategy before or after initiating CRRT is currently established.

High HR is known to be associated with increased morbidity and mortality, which has been demonstrated in the general population [15] and patients with various diseases, such as heart failure [16], ischemic heart disease [17], atrial fibrillation [18], stroke [19], and chronic obstructive pulmonary disease [20]. The relationship has been also consistent in cases of chronic kidney disease [21]. The overall trend for mortality depending on HR seemed to be linear, similar to previous study results. In this respect, the present results focusing on patients with AKI on CRRT support the current clinical context, that high HR should be considered to increase mortality risk.

The relationship between high HR and mortality can be explained by the following issues. High HR is speculated to increase mortality by increasing the sympathetic activity and promoting atherosclerosis in vessels [22]. In addition, high HR decreases tissue perfusion [23], which eventually results in ischemic damage to vital organs. CRRT aggravates hemodynamic instability, which can also help clarify the observation between HR and mortality outcome despite the cohort with extremely high mortality rate. However, the above issues had not been suggested in the setting of CRRT. Future studies are necessary to explore the underlying mechanisms in the CRRT setting.

Although the present results are informative, the study has some limitations. First, the study design was restricted to observing correlations, and this prevented us from drawing a causal relationship. Second, the overall mortality was significantly high, and this might affect the analysis of weaning such that certain patients died before considering the weaning potential. Third, the single-center design requires that the data be validated in other cohorts, although the sample size was large. Finally, unevenly distributed characteristics of patients (e.g., small proportion of chronic kidney disease in the death group) should be carefully considered in the present analyses.

The predictive model of mortality has not been established in the case of CRRT. This issue makes clinical decisions difficult, especially considering the increasing use of CRRT. In this respect, HR as a mortality-related factor in this subset might be a great concern. The present study did not suggest the proper method to monitor HR after CRRT or the adequacy of measuring HR only once. Nevertheless, the results form a basis for later studies setting up a predictive model for CRRT-related mortality.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] Hoste EA, Schurgers M: Epidemiology of acute kidney injury: how big is the problem? *Crit Care Med* 36(4 Suppl):S146-

S151, 2008

[2] Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF; Hemodiafe Study Group: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 368:379-385, 2006

[3] Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R: Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med* 36:610-617, 2008

[4] Santiago MJ, López-Herce J, Urbano J, Solana MJ, del Castillo J, Ballestero Y, Botrán M, Bellón JM: Clinical course and mortality risk factors in critically ill children requiring continuous renal replacement therapy. *Intensive Care Med* 36:843-849, 2010

[5] Maccariello E, Valente C, Nogueira L, Bonomo H, Ismael M, Machado JE, Baldotto F, Godinho M, Valença R, Rocha E, Soares M: SAPS 3 scores at the start of renal replacement therapy predict mortality in critically ill patients with acute kidney injury. *Kidney Int* 77:51-56, 2010

[6] Finkel KW, Podoll AS: Complications of continuous renal replacement therapy. *Semin Dial* 22:155-159, 2009

[7] Prasad B, Urbanski M, Ferguson TW, Karreman E, Tangri N: Early mortality on continuous renal replacement therapy (CRRT): the prairie CRRT study. *Can J Kidney Health Dis* 3:36, 2016

[8] Chou CY, Yeh HC, Chen W, Liu JH, Lin HH, Liu YL, Yang YF, Wang SM, Huang CC: Norepinephrine and hospital mortality in critically ill patients undergoing continuous renal replacement therapy. *Artif Organs* 35:E11-E17, 2011

[9] Zhang D, Shen X, Qi X: Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ* 188:E53-E63, 2016

[10] Morcet JF, Safar M, Thomas F, Guize L, Benetos A: Associations between heart rate and other risk factors in a large French population. *J Hypertens* 17:1671-1676, 1999

[11] Tverdal A, Hjellvik V, Selmer R: Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379,843 men and women aged 40-45 years. *Eur Heart J* 29:2772-2781, 2008

[12] Wannamethee G, Shaper AG, Macfarlane PW: Heart rate, physical activity, and mortality from cancer and other non-cardiovascular diseases. *Am J Epidemiol* 137:735-748, 1993

[13] Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med* 13:818-829, 1985

[14] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22:707-710, 1996

[15] Ho JE, Larson MG, Ghorbani A, Cheng S, Coglianese EE, Vasan RS, Wang TJ: Long-term cardiovascular risks associated with an elevated heart rate: the Framingham Heart Study. *J Am Heart Assoc* 3:e000668, 2014

[16] Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators: Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 376:886-894, 2010

[17] Ho JE, Bittner V, Demicco DA, Breazna A, Deedwania PC, Waters DD: Usefulness of heart rate at rest as a predictor of mortality, hospitalization for heart failure, myocardial infarction, and stroke in patients with stable coronary heart disease (Data from the Treating to New Targets [TNT] trial). *Am J Cardiol* 105:905-911, 2010

[18] Steinberg BA, Kim S, Thomas L, Fonarow GC, Gersh BJ, Holmqvist F, Hylek E, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel JA, Chang P, Peterson ED, Piccini JP; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients: Increased heart rate is associated with higher mortality in patients with atrial fibrillation (AF): results from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF). *J Am Heart Assoc* 4:e002031, 2015

[19] Erdur H, Scheitz JF, Grittner U, Laufs U, Endres M, Nolte CH: Heart rate on admission independently predicts in-hospital mortality in acute ischemic stroke patients. *Int J Cardiol* 176:206-210, 2014

[20] Warnier MJ, Rutten FH, de Boer A, Hoes AW, De Bruin ML: Resting heart rate is a risk factor for mortality in chronic obstructive pulmonary disease, but not for exacerbations or pneumonia. *PLoS One* 9:e105152, 2014

[21] Brotman DJ, Bash LD, Qayyum R, Crews D, Whitsel EA, Astor BC, Coresh J: Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol* 21:1560-1570, 2010

[22] Robinson BF, Epstein SE, Beiser GD, Braunwald E: Control

of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. *Circ Res* 19:400-411, 1966

[23] Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, Struijker-Boudier HA: Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 118:968-976, 2008