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Comparison of Plasma N-Terminal Pro-B-Type Natriuretic Peptide Levels Between European and Japanese Patients with Acute Heart Failure: An International Study

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Plasma biomarkers levels, essential for diagnosing cardiovascular diseases, may vary by ethnicity. In this international prospective study, we compared plasma biomarker levels between European and Asian patients with clinically similar acute heart failure (AHF). Data were collected on emergency admission for acute dyspnea. Blood samples were obtained within 4 hrs of presentation and analyzed for N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin-T, growth differentiation factor 15, interleukin-6, and C-reactive protein levels. Overall, 907 AHF patients were enrolled; of which, 135 (15%) were Japanese, and 772 (85%) were European. NT-proBNP levels were significantly higher in Japanese than in Europeans [4,060 ng/L (interquartile range (IQR) 2,081–12,218) vs. 3,390 ng/L (IQR 1,410–7,682), $P=0.004$]. After propensity score matching (PSM), no biomarker levels differed significantly. After stratification according to left ventricular ejection fraction (LVEF) at admission, higher NT-proBNP levels were observed in Japanese AHF patients with LVEF >50% ($P=0.02$) than in European patients. After PSM, the difference was insignificant ($P=0.35$). In Asian and Caucasian AHF patients with similar clinical profiles, plasma cardiovascular biomarker levels did not differ significantly, regardless of LVEF, suggesting that NT-proBNP and related biomarkers can be applied across these ethnicities.

Key Words: Biomarkers, Ethnicity, Europe, Japan, NT-proBNP

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Acute heart failure (AHF), defined as the rapid onset or worsening of heart failure (HF) symptoms, requires urgent treatment [1]. Accurate diagnosis is critical, and natriuretic peptides (NPs) are essential in HF diagnostic algorithms [2]. Besides modest interpatient variability, several other factors, including ethnicity [3, 4], can affect NP levels. Asian-American and African-Ameri-

can patients have been shown to have higher B-type NP (BNP) levels than Caucasian patients [3], whereas N-terminal pro-BNP (NT-proBNP) levels have been reported to be similar in stable HF patients in Asian and Western settings [4]. Notably, data on Asian populations are scarce, and the accuracy of NP thresholds in multiethnic populations and the potential underlying disparities remain to be studied. To the best of our knowledge, no prior research has evaluated NP levels in European and Asian AHF patients with comparable clinical features. Thus, we conducted an international, prospective, observational cohort study comparing cardiovascular biomarker profiles between these populations to assess the potential impact of ethnic background on biomarker levels.

A total of 1,668 patients were initially evaluated for inclusion. After excluding those with missing data for any study variable, 907 AHF patients were retained in the final analysis [135 (15%) from Japan and 772 (85%) from Europe]. Japanese patients were enrolled at Nippon Medical School Musashikosugi Hospital (Kawasaki, Japan) and Kawaguchi Cardiovascular and Respiratory Hospital (Kawaguchi, Japan), while European patients were enrolled from two pre-registered prospective studies: the Lithuanian Echocardiography Study of Dyspnoea in Acute Settings (NCT03048032) and Diagnostic and Prognostic Value of New Biomarkers in Patients With Heart Disease study (NCT01374880), conducted at multiple European sites. The study was approved by local ethics committees: Lithuanian Bioethics Committee (No. L-15-01), Comité d'Evaluation de l'Ethique des Projets de Recherche Biomédicale (CEERB) (No. 10-017), Nippon Medical School Musashi-Kosugi Hospital (No. 220-24-20) and Kawaguchi Cardiovascular and Respiratory Hospital (No. 2016-003). Informed consent was obtained from all patients.

AHF was defined according to European Society of Cardiology guidelines [1]. Clinical and biological data were collected upon admission into the emergency department for acute dyspnea by reviewing electronic medical records. Blood samples were collected within 4 hrs of presentation, stored at −80°C, and transferred to INSERM UMR-S 942 (Paris, France) for centralized biomarker analyses, including single baseline measurements of NT-proBNP, high-sensitivity troponin-T (hs-TnT), growth differentiation factor 15 (GDF-15), interleukin-6 (IL-6), and C-reactive protein (CRP) levels, using commercial assays (Roche Diagnostics, Mannheim, Germany, Europe). NT-proBNP, hs-TnT, GDF-15, and IL-6 levels were measured using electrochemiluminescence immunoassays on a Cobas E801 analyzer (Roche Diagnostics, Meylan, France). CRP concentrations were measured using the Tina-quant CRP-Gen.3 immunoturbidimetric assay on a Cobas c701 analyzer (Roche Diagnostics). Analytical performance metrics (including limits of detection and measurement ranges) were provided by the manufacturer. CVs, obtained through internal QC testing during the study, were <5% and in accordance with our laboratory standards.

Baseline characteristics were compared using Pearson's chi-squared or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous or ordinal variables, as appropriate. Biomarkers levels were compared between groups using both the Wilcoxon rank-sum test and standardized mean differences (SMDs) with 95% confidence intervals. An absolute SMD <0.1 was considered indicative of adequate balance. Propensity score matching (PSM) was conducted using logistic regression to estimate scores based on age, sex, body mass index (BMI), left ventricular ejection fraction (LVEF), systolic blood pressure, heart rate, estimated glomerular filtration rate, history of diabetes mellitus, chronic HF, atrial fibrillation, and coronary artery disease. Patients were matched in a 3:1 ratio via nearest-neighbor matching with a caliper of 0.8 SDs of the logit of the propensity score. For sensitivity analysis, multivariable logistic regression was used to assess the association between ethnicity and NT-proBNP levels after matching, adjusting for renal function (serum creatinine), age, and BMI, which are known clinical confounders influencing NT-proBNP levels.

Several differences were noted prior to PSM. Japanese patients had significantly lower Hb levels [119 g/L (IQR 100.5, 134.0) vs. 130 g/L (IQR 115.0, 143.0), $P<0.001$]. Median LVEF was 40% (IQR 20, 54) in European patients and 45% (IQR 32, 60) in Japanese patients ($P<0.001$). Japanese patients were less frequently treated with standard HF medications at discharge [beta-blockers: 12 (8.9%) vs. 450 (59%), $P<0.001$, renin-angiotensin antagonists: 52 (39%) vs. 395 (52%), $P=0.02$]. After 3:1 PSM, differences became either non-significant or were markedly reduced (Table 1, Supplemental Data Table S1, and Supplemental Data Fig. S1).

NT-proBNP levels were significantly higher in Japanese AHF patients than in their European counterparts [4,060 ng/L (IQR 2,081, 12,218) vs. 3,390 ng/L (IQR 1,410, 7,682), $P=0.004$] (Table 2). After PSM, NT-proBNP levels showed no significant difference between the two groups [4,040 ng/L (IQR 2,084, 11,356) in Japan vs. 3,722 ng/L (IQR 1,324, 8,727), $P=0.083$], with a SMD of −0.09, suggesting an adequate balance between the cohorts. After stratification according to LVEF at admission (<40%, 40%–50%, and >50%), NT-proBNP levels were significantly higher in Japanese AHF patients, particularly in the group with LVEF >50% (N=118 vs. 47, $P=0.02$) (Fig. 1A), with no sig-

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Table 1. Patient characteristics at baseline before and after propensity score matching

Patient characteristics	Before propensity score matching					After propensity score matching				
	N	Overall N=907*	Europe N=772*	Japan N=135*	*P*†	N	Overall N=346*	Europe N=249*	Japan N=97*	*P*†
Age (yrs)	907	73 [64, 81]	72 [63, 80]	79 [70, 87]	**<0.001**	346	75 [65, 83]	74 [65, 82]	78 [64, 86]	**0.032**
Sex (male)	907	520 (57%)	443 (57%)	77 (57%)	>0.9	346	204 (59%)	148 (59%)	56 (58%)	0.2
BMI	636	28 [24, 33]	30 [25, 35]	23 [21, 26]	**<0.001**	346	27.1 [22.8, 28.3]	28.3 [23.3, 28.3]	24.8 [22.0, 27.9]	**<0.001**
Comorbidities										
DM	888	256 (29%)	208 (28%)	48 (36%)	**0.045**	346	115 (33%)	83 (33%)	32 (32%)	0.6
Hypertension	896	737 (82%)	650 (85%)	87 (65%)	**<0.001**	343	261 (76%)	197 (80%)	64 (67%)	**<0.001**
COPD	888	90 (10%)	86 (11%)	4 (3.0%)	**0.003**	338	28 (8.3%)	26 (11%)	2 (2.1%)	**0.005**
CHF	888	657 (74%)	622 (82%)	35 (26%)	**<0.001**	346	176 (51%)	144 (58%)	32 (33%)	**<0.001**
CAD	890	361 (41%)	339 (45%)	22 (16%)	**<0.001**	346	87 (25%)	69 (28%)	18 (19%)	0.065
Chronic atrial fibrillation	888	489 (55%)	443 (59%)	46 (34%)	**<0.001**	338	156 (46%)	121 (50%)	35 (36%)	0.12
Clinical characteristics										
Systolic blood pressure (mmHg)	895	140 [123, 60]	140 [121, 160]	147 [129, 173]	**<0.001**	346	140 [124, 160]	140 [122, 160]	142 [126, 169]	0.6
Diastolic blood pressure (mmHg)	893	80 [70, 91]	80 [70, 90]	86 [74, 101]	**0.007**	344	81 [73, 92]	80 [73, 90]	85 [73, 99]	0.7
Heart rate (/min)	894	89 [72, 106]	86 [71, 103]	97 [80, 117]	**<0.001**	346	90 [74, 110]	88 [72, 109]	96 [81, 116]	0.064
LVEF (%)	557	40 [26, 55]	40 [25, 55]	45 [32, 60]	**<0.001**	346	40 [38, 50]	40 [40, 46]	41 [32, 55]	0.062
Hb (g/L)	872	128 [113, 142]	130 [115, 143]	119 [101, 134]	**<0.001**	346	127 [111, 148]	128 [115, 141]	121 [102, 138]	**<0.001**
Sodium (mmol/L)	828	139 [136, 141]	139 [136, 141]	139 [136, 141]	>0.9	324	139 [136, 141]	139 [136, 142]	139 [136, 141]	0.7
Creatinine (μmol/L)	874	101 [81, 135]	100 [81, 132]	107 [82, 158]	0.12	338	99 [81, 136]	98 [80, 130]	106 [83, 154]	0.091
eGFR (mL/min/1.73 m^2)	874	43 [32, 56]	44 [32, 56]	42 [24, 56]	**0.014**	346	47 [47]	47 [47]	47 [33, 58]	0.7
Blood sugar (mmol/L)	719	6.3 [5.5, 8.0]	6.1 [5.4, 7.4]	7.7 [6.1, 9.9]	**<0.001**	288	6.5 [5.5, 8.6]	6.1 [5.3, 7.8]	7.3 [6.1, 9.9]	**<0.001**
Medical therapy										
β-blocker at admission	899	462 (51%)	450 (59%)	12 (8.9%)	**<0.001**	346	139 (40%)	129 (52%)	10 (10%)	**<0.001**
ACEI/ARB2 at admission	891	447 (50%)	395 (52%)	52 (39%)	**0.006**	341	159 (47%)	120 (49%)	39 (41%)	0.2
Aldosterone blocker at admission	899	206 (23%)	189 (25%)	17 (13%)	**0.002**	346	64 (18%)	52 (21%)	12 (12%)	0.2

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Table 1. Continued

Patient characteristics	Before propensity score matching					After propensity score matching				
	N	Overall N=907*	Europe N=772*	Japan N=135*	$P^{\dagger}$	N	Overall N=346*	Europe N=249*	Japan N=97*	$P^{\dagger}$
Diuretics at admission	892	476 (53%)	428 (56%)	48 (36%)	**<0.001**	341	153 (45%)	116 (47%)	37 (39%)	0.3
Nitrate at admission	899	68 (7.6%)	57 (7.5%)	11 (8.1%)	0.8	346	21 (6.1%)	11 (4.4%)	10 (10%)	0.052
Aspirin at admission	899	223 (25%)	206 (27%)	17 (13%)	**<0.001**	346	76 (22%)	62 (25%)	14 (14%)	**0.019**
Statin at admission	899	133 (15%)	114 (15%)	19 (14%)	0.8	346	40 (12%)	27 (11%)	13 (13%)	0.4
β-blocker at discharge	875	604 (69%)	531 (72%)	73 (54%)	**<0.001**	336	211 (63%)	157 (66%)	54 (56%)	0.2
ACEI/ARB2 at discharge	862	559 (65%)	461 (63%)	98 (74%)	**0.020**	326	217 (67%)	145 (63%)	72 (76%)	0.2
Aldosterone blocker at discharge	875	357 (41%)	292 (39%)	65 (48%)	0.059	336	122 (36%)	77 (32%)	45 (46%)	**0.001**
Outcomes										
Time of hospitalization	903	8 [2, 13]	7 [1, 11]	15 [9, 25]	**<0.001**	342	9 [4, 14]	7 [1, 11]	15 [9, 26]	**<0.001**
Death in hospital	907	38 (4.2%)	30 (3.9%)	8 (5.9%)	0.3	346	10 (4.0%)	4 (3.2%)	6 (4.8%)	0.2

*Values are expressed as median and interquartile range [IQR], or as count and percentage (%), as appropriate.
†Categorical variables were compared using Pearson's chi-squared or Fisher's exact test, as appropriate; continuous and ordinal variables were analyzed using the Wilcoxon rank-sum test. Significance was set to a two-sided $P<0.05$; Significant values are highlighted in bold.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; CI, confidence interval; CHF, chronic heart failure; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; sBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ACEI, angiotensin-converting enzyme inhibitors; ARB2, angiotensin II receptor blockers.

nificant differences in the <40% (N=208 vs. 45, $P=0.97$) and 40%–50% subgroups (N=100 vs. 29, $P=0.11$). However, post-PSM NT-proBNP levels were not significantly different in any LVEF subgroup (<40%, N=55 vs. 36, $P=0.79$; 40%–50%, N=137 vs. 26, $P=0.21$; >50%, N=51 vs. 34, $P=0.36$) (Fig. 1B).

hs-TnT, GDF-15, IL-6, and CRP levels did not significantly differ between Japanese and European AHF patients at baseline or after PSM. The sensitivity analysis revealed that, after adjusting for renal function (serum creatinine), age, and BMI, the NT-proBNP levels did not differ significantly between Japanese and European patients (estimate=0.935, $P=0.666$; Supplemental Data Table S2).

This study demonstrated that biomarker levels, particularly NT-proBNP levels, do not differ significantly between European and Japanese AHF patients. Analyses based on LVEF subclasses also did not reveal significant differences. However, importantly, our study was underpowered to conclusively detect differences among the LVEF subgroups.

Precipitating factors in AHF show ethnic differences [5]; for instance, anemia, primarily caused by iron deficiency, is more prevalent in the Japanese population [6], as also observed in our cohort. Iron deficiency affects up to 80% of AHF patients and may act as a triggering factor [1].

As for HF medications, the higher rate of beta-blocker use at admission in European patients likely reflects a greater prevalence of chronic HF in this group, as opposed to the more frequent *de novo* presentations in Japanese patients. However, this difference is unlikely to have significantly influenced NT-proBNP levels, particularly given the absence of between-group differences in diuretic prescription at admission after matching, suggesting comparable disease severity at presentation. Regarding medications for HF at discharge, the observed differences should not be interpreted in the context of different clinical guidelines. We analyzed data collected between 2011 and 2017, when older HF guidelines comparable between regions

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Table 2. Comparison of biomarker levels per region before and after propensity score matching

Parameter	Before propensity score matching							After propensity score matching						
	N	Overall N=907*	Europe N=772*	Japan N=135*	SMD†	95% CI‡	P§	N	Overall N=346*	Europe N=249*	Japan N=97*	SMD†	95% CI‡	P§
NT-proBNP (ng/L)	877	3,522 [1,471, 7,876]	3,390 [1,410, 7,682]	4,060 [2,081, 12,218]	-0.21	-0.40, -0.03	0.004	339	3,833 [1,630, 9,279]	3,722 [1,324, 8,727]	4,040 [2,084, 11,356]	-0.09	-0.33, 0.14	0.08
Troponin-T (pg/mL)	165	47 [26, 91]	44 [24, 61]	53 [26, 94]	-0.25	-0.64, 0.13	0.2	114	47 [25, 102]	47 [30, 112]	47 [24, 91]	-0.24	-0.75, 0.28	0.8
CRP (mg/L)	163	5 [2, 19]	5 [3, 15]	5 [2, 20]	-0.04	-0.43, 0.34	0.8	112	5 [2, 18]	5 [2, 15]	5 [2, 19]	0.13	-0.39, 0.64	0.7
GDF-15 (pg/mL)	66	3,753 [2,424, 5,894]	3,286 [2,252, 6,119]	4,106 [2,562, 5,487]	-0.10	-0.58, 0.38	0.6	43	4,093 [2,481, 5,563]	2,981 [2,121, 5,638]	4,202 [2,762, 5,487]	-0.38	-1, 0.23	0.2
IL-6 (pg/mL)	165	16 [9, 39]	11 [8, 28]	17 [9, 47]	-0.21	-0.59, 0.17	0.2	114	15 [9, 45]	10 [9, 28]	17 [9, 48]	-0.21	-0.73, 0.30	0.3

*Values are expressed as median and [IQR].
†‡SMDs and 95% confidence intervals were calculated to assess differences in continuous variables between groups; an absolute SMD of < 0.1 was considered indicative of adequate balance.
§Wilcoxon rank-sum test.
Significance was set to a two-sided $P < 0.05$.
Abbreviations: SMD, standard mean difference; NT-proBNP, N-terminal pro-B-type natriuretic peptide; GDF-15, growth/differentiation factor 15; IL-6, interleukin 6; BMI, body mass index; LVEF, left ventricular ejection fraction; sBP, HR, eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHF, chronic heart failure; CAD, coronary artery disease.

were in use. Hence, the observed differences in medical therapy cannot be attributed to variations in treatment indications. European patients better adhered to the guidelines from that period, as opposed to the suboptimal management among Japanese HF patients. Although data on sodium glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin receptor/neprilysin inhibitor (ARNI) use were not available for our cohorts, these treatments represent key components of modern HF management and may influence NT-proBNP levels. NT-proBNP levels do not typically increase through neprilysin inhibition during ARNI treatment; instead, persistently elevated values are associated with worse outcomes because of ongoing congestion or disease progression [7]. In contrast, SGLT2is lower NT-proBNP levels, likely through diuretic effects exerted both alone and synergistically with other HF therapies and favorable cardiac remodeling [8, 9].

Underutilization of guideline-directed medical therapy (GDMT) has been observed across ethnic groups [10], and achieving adequate prescription and dose titration of GDMT among demographic groups remains a challenge in ensuring quality HF care. A Japanese observational study revealed a reduced use of cardioprotective medications for HF with reduced ejection fraction at discharge [11].

Our study had some limitations. First, this was an observational study, which may have led to selection and confounding biases. Second, in the European database, ethnicities were not specified. While this reflects real-world European clinical practice, with patients of various ethnicities, further large studies from both regional and ethnic perspectives are required. Third, the sample size was small, limiting representativeness and statistical power. Fourth, the absence of healthy control data limited contextualization of biomarker levels within normal ranges. Fifth, the statistical power was insufficient to reliably detect differences within LVEF subgroups, which may affect interpretation of subgroup analyses. Finally, data regarding medical therapy did not reflect current guidelines and clinical practice, although we believe that comparable treatment exposure would not have substantially affected our findings. In this regard, studies using contemporary data will provide more insights.

In conclusion, NT-proBNP levels do not differ significantly between Caucasian and Asian AHF patients with similar clinical presentations, regardless of LVEF. Our results support that NT-proBNP levels in AHF patients can be interpreted without requiring ethnicity-specific adjustments in these populations.

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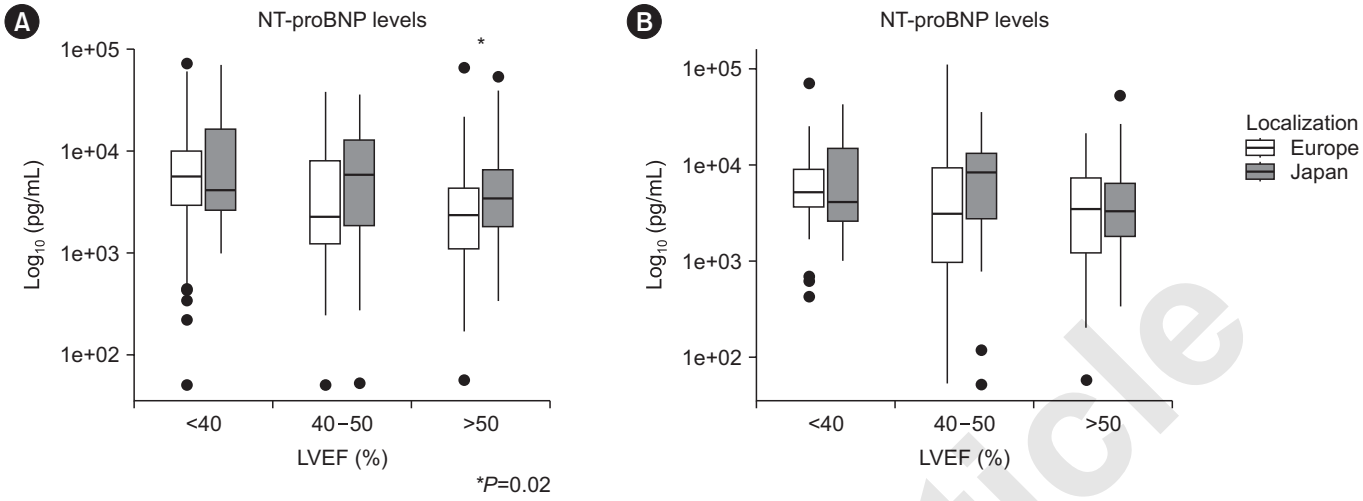

Fig. 1. Comparison of NT-proBNP levels across LVEF subgroups before (A) and after (B) propensity score matching.
Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2025.0232.

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AUTHOR CONTRIBUTIONS

Mebazaa A, Deniau B, and Ishihara S contributed to the conception and design of the study; Bruno J and Daghmouri A performed the statistical analysis and interpreted the results; Gobeaux C was responsible for biomarker measurements and interpretation of analytical results; Čerlinskaitė-Bajorė K, Čelutkienė J, and Sato N provided the clinical data; Bruno J drafted the manuscript; Asakage A and Takagi K contributed to review and editing of the manuscript; Mebazaa A and Deniau B supervised the study. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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