Clinical Determinants of Quality of Life in Patients With Acute Decompensated Heart Failure With Preserved Ejection Fraction: Insights From the PURSUIT-Heart Failure With Preserved Ejection Fraction Registry

Masahiro Seo (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Tetsuya Watanabe (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Takahisa Yamada (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Masamichi Yano (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Takaharu Hayashi (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Akito Nakagawa (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Yusuke Nakagawa (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Shunsuke Tamaki (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Yohei Sotomi (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Shungo Hikoso (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Daisaku Nakatani (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Masatake Fukunami (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Yasushi Sakata (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Yoshio Yasumura (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Akito Nakagawa (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)
Takahisa Yamada (Division of Cardiology, Osaka General Medical Center, 3-1-56 Mandai-Higashi, Sumiyoshi-ku, Osaka 558-8558, Japan. Email: roland-dyens@hotmail.co.jp)

Improvement of quality of life (QOL) is one of the most important clinical end points for patients with heart failure (HF). As our society continues to age, patients with HF are placing increasing value on better QOL over prolonged survival. Thus, physicians should place increasing awareness toward improving QOL in the management of HF.

The prevalence of HF with preserved ejection fraction (HFpEF) is rapidly increasing worldwide and the condition is becoming a growing issue as patients with HFpEF are generally old and often have multiple comorbidities. It is, therefore, clinically relevant to identify aggravating factors of QOL among cardiac factors and noncardiac comorbidities comprehensively, to specify appropriate therapeutic targets in HFpEF. Although several previous studies of HFpEF in the United States have already identified clinical correlates of adverse QOL, the results might vary depending on geography, considering the wide diversity and regionality of HFpEF. Therefore, we aimed to identify the factors associated with impaired QOL in Japanese patients with HFpEF.
that the subjects gave informed consent. Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions. However, the study materials that support the findings of this study and the methods used in the analyses will be provided by the corresponding author upon reasonable request.

Between June 2016 and September 2020, a total of 864 patients were enrolled in the present study (mean age: 81 years, the proportion of female: 55%, mean body mass index: 22 kg/m²). The study population was divided into tertiles based on their EQ-5D-5L score as follows: low EQ-5D-5L 0.038 to 0.664 (n=287), middle EQ-5D-5L 0.665 to 0.867 (n=293), and high EQ-5D-5L 0.871 to 1.000 (n=284). The Jonckheere-Terpstra test and Cochran-Armitage test showed that low EQ-5D-5L scores were significantly associated with higher age (\(P<0.01\)), higher female rate (\(P<0.01\)), higher NT-proBNP level (\(P<0.01\)), lower geriatric nutritional risk index (\(P<0.01\)), and higher clinical frailty scale (\(P<0.01\)).

The result of multivariable ordinal logistic regression analysis for the identification of factors associated with impaired QOL was shown in the Figure. Age (\(P<0.01\)), female sex (\(P<0.01\)), and log-transformed NT-proBNP (\(P<0.01\)) were significantly associated with impaired QOL. Notably, noncardiac factors, such as malnutrition (\(P=0.03\)) and frailty (clinical frailty scale; \(<0.01\)) were significantly associated with worse QOL. On the other hand, cardiac factors, such as NYHA class, AF, LVDd, TRPG, and cardiac index had no significant association after multivariable adjustment.

One of the distinctive results of the present study was a significant association between impaired QOL and noncardiac factors, such as higher age and malnutrition. This result was in contrast with previous studies in the United States, which showed that young age and obesity were significant predictors of adverse QOL in patients with HFpEF. These contradictory results could be derived from differences in HFpEF phenotype based on geographic differences. Although participants in HFpEF studies in the United States have contained a large proportion of patients with the young obese phenotype of HFpEF, our cohort was mainly composed of a thin elderly female phenotype with high comorbidity burden.

### Figure

**Figure. Multivariable ordinal logistic regression model for the identification of factors associated with impaired quality of life (QOL).**

| Covariates                        | adjusted OR (95% CI) | p-value |
|-----------------------------------|----------------------|---------|
| **Baseline factors**              |                      |         |
| Age (per 5-years)                 | 1.22 (1.09-1.37)     | <0.01   |
| Female sex                        | 1.78 (1.23-2.57)     | <0.01   |
| **Cardiac factors**               |                      |         |
| Log NT-proBNP                     | 1.31 (1.10-1.55)     | <0.01   |
| LVDd (per 5mm)                    | 1.17 (0.99-1.37)     | 0.06    |
| NYHA class (\(\geq 3\))          | 0.81 (0.39-1.71)     | 0.57    |
| AF                                | 0.73 (0.51-1.04)     | 0.08    |
| TRPG (per 5mmHg)                  | 0.94 (0.86-1.03)     | 0.18    |
| Cardiac index                     | 0.91 (0.75-1.11)     | 0.37    |
| **Non-cardiac comorbidities**     |                      |         |
| Clinical frailty scale (per 2unit) | 2.00 (1.60-2.52)   | <0.01   |
| *Malnutrition*                    | 1.52 (1.05-2.22)     | 0.03    |
| Log CRP                           | 1.10 (0.98-1.24)     | 0.11    |
| Stroke                            | 1.47 (0.91-2.39)     | 0.12    |
| eGFR (per 10ml/min/1.73m²)        | 1.09 (0.98-1.22)     | 0.11    |
| **Anemia**                        | 1.12 (0.76-1.67)     | 0.57    |
| DM                                | 1.00 (0.70-1.43)     | 0.99    |
| COPD                              | 0.87 (0.47-1.61)     | 0.66    |
| HT                                | 0.80 (0.50-1.27)     | 0.34    |

*AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; DM, diabetes; eGFR, estimated glomerular filtration rate; HT, hypertension; Log CRP, log-transformed C-reactive protein; Log NT-proBNP, log-transformed N-terminal pro-B-type natriuretic peptide; LVDd, left ventricular end-diastolic dimension; NYHA, New York Heart Association; OR, adjusted odds ratio; and TRPG, tricuspid regurgitant pressure gradient. *Malnutrition was defined as a geriatric nutritional risk index below 92, according to previous studies on HFpEF. **Anemia was defined as hemoglobin <13 mg/dL for men and <12 mg/dL for women.
Accordingly, determinants of adverse QOL may be completely different depending on phenotype of HFP EF.

The present study also showed that frailty was one of the strongest correlated factors of impaired QOL. Together, our findings suggest that aging, malnutrition, and the subsequent progression of frailty could be predominant factors of adverse QOL in Japanese patients with HFP EF. Therefore, malnutrition and frailty are potential therapeutic targets for improving QOL in addition to the optimization of HF therapies, considering the fact that NT-proBNP level was also a significant factor associated with worse QOL. Although weight loss is a postulated solution for improving QOL in patients with the obese phenotype of HFP EF, therapeutic strategies to ameliorate QOL in Japanese patients with HFP EF seem to go in the opposite direction. Thus, it is important to be cautious of patients’ nutritional status in daily practice. Moreover, establishment of effective nutritional support therapies may also be beneficial.

Major limitations are based on the observational nature of the study. It was difficult to clarify the causal relationship between impaired QOL and several covariates. Further interventional studies are required to clarify whether nutritional support therapies can improve QOL in patients with HFP EF.

In conclusion, aging, female sex, NT-proBNP, and especially noncardiac comorbidities, such as malnutrition and frailty were significant factors associated with impaired QOL in Japanese patients with HFP EF.

ARTICLE INFORMATION

Affiliations
Division of Cardiology, Osaka General Medical Center, Japan (M.S., T.W., T.Y., M.F.). Division of Cardiology, Osaka Rosai Hospital, Japan (M.Y.). Division of Cardiology, Osaka Police Hospital, Japan (T.H.). Division of Cardiovascular Medicine, Amagasaki-Chuo Hospital, Hyogo, Japan (A.N., Y.Y.). Division of Cardiology, Kawanishi City Hospital, Hyogo, Japan (Y.N.). Department of Cardiology, Rinku General Medical Center, Izumisano, Osaka, Japan (S.T.). Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Japan (Y. Sotomi, S.H., D.N., Y. Sakata). Division of Cardiovascular Medicine, Osaka Police Hospital, Japan (T.H.). Division of Cardiology, Rinku General Medical Center, Izumisano, Osaka, Japan (S.T.). Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Japan (Y. Sotomi, S.H., D.N., Y. Sakata). Department of Medical Informatics, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Japan (A.N.).

Acknowledgments
The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their interpretation.

Sources of Funding
This work was funded by Roche Diagnostics KK and Fuji Film Toyama Chemical Co Ltd.

Disclosures
Dr Nakatani has received honoraria from Roche Diagnostics. Dr Hikoso has received personal fees from Daiichi Sankyo Company, Bayer, Astellas Pharma, Pfizer Pharmaceuticals, and Boehringer Ingelheim Japan and grants from Roche Diagnostics, FUJIFILM Toyama Chemical, and Actelion Pharmaceuticals. Dr Sotomi received research grants from Abbott Medical Japan and speaker honoraria from Abbott Medical Japan, Boston Scientific Japan, TERUMO, Japan Lifeline, Biosensors, and Medtronic, and is an endowed chair funded by TOA EY. Dr Sakata has received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, and Actelion Pharmaceuticals and grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, and Biotronik. The other authors have no conflicts of interest to disclose.

REFERENCES
1. Brunner-La Rocca HP, Rickenbacher P, Muzzarelli S, Schindler R, Maeder MT, Jeker K, Ioowski W, Leverthal ME, Pfister G, Osswald S, et al. End-of-life preferences of elderly patients with chronic heart failure. Eur Heart J. 2012;33:752–759. doi: 10.1093/eurheartj/ehr404
2. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, Dunlay S, McNulty S, Chakraborty H, Stevenson LW, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. Eur J Heart Fail. 2020;22:1009–1018. doi: 10.1002/ejhf.11788
3. Suna S, Hikoso S, Yamada T, Uematsu M, Yasumura Y, Nakagawa A, Takeda T, Kojima T, Kida H, Oeun B, et al; OCVC-Heart Failure Investigators. Study protocol for the PURSUIT-HFpEF study: a prospective, multicenter, observational study of patients with heart failure with preserved ejection fraction. BMJ Open. 2020;10:e038294. doi: 10.1136/bmjopen-2020-038294
4. Minamisawa M, Seidelmann SB, Ciglletti B, Hegde SM, Shah AM, Desai AS, Lewis EF, Shah SJ, Sveitzer NK, Fang JC, et al. Impact of malnutrition using geriatric nutritional risk index in heart failure with preserved ejection fraction. JACC Heart Fail. 2019;7:664–676. doi: 10.1016/j.jchf.2019.04.020
5. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–1736. doi: 10.1007/s11136-011-9903-x