Association between multimorbidity, self-rated health and life satisfaction among independent, community-dwelling very old persons in Japan: longitudinal cohort analysis from the Kawasaki Ageing and Well-being Project

Takayuki Ando,1 Yoshinori Nishimoto,2 Takumi Hirata,3 Yukiko Abe,4 Midori Takayama,5 Takashi Maeno,6 Seitaro Fujishima,1 Toru Takebayashi,7 Yasumichi Arai 4

ABSTRACT

Objective This study aimed to identify associations between multimorbidity and subjective health outcomes among the very old persons, after adjusting for coexisting conditions such as frailty and depression.

Study setting and participants This was an observational cross-sectional study involving 1012 independent, community-dwelling very old persons (507 men, 505 women; aged 85–89 years) in Kawasaki city, Japan.

Outcome measures The primary outcome was the association of subjective health with each chronic condition.

Results The prevalence of multimorbidity (≥2 conditions) was 94.7%, and the average number of chronic conditions was 4.47 ± 1.9. Multimorbidity was significantly associated with poor SRH in the adjusted model only when six or more chronic conditions were present (OR 4.80; 95% CI 1.34 to 17.11; p=0.016). Cerebrovascular disease, heart disease, respiratory disease, connective tissue disease and arthritis showed significant associations with poor SRH after multivariate adjustment. Sex-specific analysis replicated associations between multimorbidity with six or more conditions and SRH in both men and women, while the diseases with the greatest impact on SRH differed between men and women. Most conditions were not associated with low satisfaction with life scale, with the exception of arthritis (OR 1.92, 95% CI 1.32 to 2.78, p=0.001).

Conclusions Multimorbidity is prevalent in the independent, community-dwelling very old persons and is associated with poor SRH when six or more conditions are present; conditions causing mobility limitations, such as cerebrovascular disease, connective tissue disease and arthritis, have a negative impact on SRH.

Strengths and limitations of this study

► The data for this study were obtained from a relatively large sample of approximately 1000 independent, community-dwelling, very old persons aged 85 years and older.

► The number of chronic diseases among the subjects was measured not only by self-report, but also by medical interviews to ensure the accuracy of the data.

► The analysis was conducted using a multivariate model that adjusted for factors that influence the health of the old, such as frailty, depression and instrumental activities of daily living.

► A stratified analysis is performed for male and female subjects to examine the effects of sex differences.

► Our inclusion criteria of only those who are independent in daily living limits the validation of the association between dementia and self-rated health.

INTRODUCTION

Multimorbidity, defined as the presence of two or more chronic conditions, has become increasingly common among older adults.1 With the rapidly ageing global population, multimorbidity is becoming a public health priority, as it is associated with an increased risk of functional decline,2 greater healthcare burden3 and increased mortality.4 The outcome measures in multimorbidity research include not only objective outcomes such as mortality and disability, but also subjective health outcomes such as quality
of life, well-being and self-rated health (SRH). SRH is an important measure of a person’s physical and psychological state, which can be surveyed with a simple question, ‘How is your health now?’ SRH has been reported to be associated with physical functioning, well-being and mortality in various countries and ages. A cohort study of postmidlife populations indicated that multimorbidity is associated with a decline in subjective health. Multimorbidity is recognised as a public health burden in Japan’s rapidly ageing society, in which life expectancy is over 80 years. The prevalence of multimorbidity is reported to increase with age, reaching 65% at 65 years and nearly 100% at 85 years. The prevalence of frailty also increases with age, and the effects of the two conditions on physical and mental health overlap. It has been reported that poor SRH and grip strength are associated with multimorbidity in the older Japanese population, suggesting that multimorbidity is linked to frailty and affects subjective health. However, little is known about the extent to which multimorbidity independently affects health and well-being in the very old persons. This study aimed to clarify the impact of multimorbidity on subjective health outcomes in very old persons aged >85 years, adjusting for frailty, depression and other potential confounders. In order to clarify the impact of each chronic condition on SRH and life satisfaction within the context of multimorbidity, a condition-specific analysis was also conducted.

**METHODS**

**Study design and data source**

The Kawasaki Ageing and Well-being Project (KAWP) is an ongoing longitudinal cohort study aiming to observe a decline of independence in very old persons who are physically independent at baseline. The inclusion criteria for the KAWP are as follows: (1) be a resident of Kawasaki city, a city with a population of 1.5 million, located in the Greater Tokyo Area and aged 85—89 years, (2) have no limitations related to basic activities of daily living (ADLs) and (3) able to visit the study site and the Kawasaki Municipal Hospitals independently. Between March 2017 and December 2018, we identified 9978 eligible individuals from the residential registry and long-term care insurance in collaboration with the Kawasaki Municipality. We sent an invitation letter to all of these individuals, and 1464 responded expressing their willingness to participate in the KAWP survey. Among the positive responders, 438 (16; not meeting inclusion criteria, 83; unable to telephone contact, 99; acute illness, 139; declined after telephone instruction, 68; unable to consent, 21; family circumstances, 12; unknown) were excluded, thus a total of 9526 individuals (513 men and 513 women) were examined at one of three Kawasaki Municipal Hospitals (Kawasaki, Ida or Tama) and enrolled in the KAWP. In the current study, we excluded 14 participants with missing values in the past and present medical history, and 1012 were included in the final analysis. Written informed consent to participate in the KAWP was obtained from all participants.

**Assessment**

The assessment questionnaires of the KAWP were designed to harmonise with the Tokyo Oldest Old Survey on Total Health and Japan Semi-supercentenarian Study, both of which are managed by the Center for Supercentenarian Medical Research, Keio University School of Medicine. The questionnaire included socio-economic status; previous medical histories and present medical conditions; current medication use; and various lifestyle factors including smoking, alcohol consumption, and physical and cognitive function. For the assessment, all the participants were interviewed and examined directly by experienced physicians. The past and present medical diagnoses included 18 categories: cerebrovascular disease, cardiac disease, hypertension, diabetes, dyslipidaemia, respiratory disease, gastrointestinal disease, renal disease, prostate disease, thyroid disease, Parkinson’s disease, connective tissue disease, eye disease, osteoporosis, arthritis, hyperuricaemia, malignancy and dementia (online supplemental table 1). Instrumental ADL (IADLs) were assessed using the Lawton scale (0–5 points), cognitive function was evaluated using the Mini-Mental State Examination (MMSE; 0–30 points), and depression was assessed using the Geriatric Depression Scale (GDS-15). Independent IADL was defined as a score of 5 points on the Lawton Scale. Frailty was evaluated using the Japanese version of the Cardiovascular Health Study (J-CHS) criteria. (0: robust, 1–2: prefrail, and 3–5: frail). Results of the GDS-15 were classified into three categories: 0–4, 5–9, and 10–15 indicated normal, mild depression, depression, respectively.

**Outcome**

Both SRH and life satisfaction were selected as the main outcomes. SRH was evaluated by asking, ‘How is your health in general?’ The response option was a five-point Likert scale, with 1 denoting very healthy and 5 denoting very unhealthy. The main outcome was poor SRH, which was defined as poor (a score of 4) or very poor (a score of 5). We used the Satisfaction with Life Scale (SWLS) as a measure of life satisfaction, which consists of five questions with seven possible rating options. The scores ranged from 5 to 35, with high scores reflecting high satisfaction. An SWLS score <20 indicated poor life satisfaction.

**Statistical analysis**

Baseline characteristics were expressed as means±SD or medians and IQRs; categorical variables were shown as numbers and proportions. Age, sex, current drinking history, current smoking history, body mass index, IADL, education (high school graduation or higher), frailty (J-CHS criteria), depression (GDS-15), and number of chronic conditions were considered independent variables. IADL, frailty and GDS were analysed as categorical
variables. We conducted univariate and multivariate logistic regression analyses to examine the association between multimorbidity and subjective health outcomes. We also performed a multivariate logistic regression analysis to examine the independent association between subjective health outcomes and each chronic condition with p values of <0.10 in the univariate analysis. We reported unadjusted and adjusted ORs and 95% CIs for poor SRH and poor life satisfaction. Supplementary analyses by stratification by sex were also performed to examine the interaction effect of sex and multimorbidity. All analyses were conducted using SPSS V.27 software (SPSS), and the results were considered statistically significant at a two-sided p<0.05.

**Patient and public involvement**

Participants (healthy older adults) and/or the public were not involved in the design, or conduct, or reporting of this study. To disseminate the results of this research, Kawasaki City and Keio University have been holding an annual public lecture since 2017, to which the participants are invited.

**RESULTS**

The characteristics of the participants are displayed in **table 1**. Most participants (86.5%) were independent of IADLs, and 13.2% met the J-CHS criteria of frailty. Further, 85.4% rated their health as moderate to very good. The mean MMSE score was 26.04, and 16.4% of the participants had an MMSE score of ≤23. The mean SWLS score was 24.95, and 70.2% scored ≥20 points. In addition, 26.9% of the participants had a GDS score of ≥5, which suggests the presence of depressive mood or depression.

A histogram of chronic conditions is shown in **figure 1**. The prevalence of multimorbidity (two or more conditions) was 94.7%, and the average number of chronic conditions was 4.47±1.94. **Figure 2** indicates the prevalence of each condition. Eye disease (75.5%), hypertension (64.1%) and gastrointestinal disease (60.0%) were the most prevalent conditions, while Parkinson’s disease (0.3%), dementia (2.5%) and connective tissue disease (3.2%) were rare in our very old cohort. The sex-specific prevalence of chronic conditions is shown in online supplemental figure 1. The prevalence of hypertension and gastrointestinal diseases did not show much difference between the sexes. Dyslipidaemia, osteoporosis, thyroid disease, arthritis and eye disease were prevalent in female participants, while hyperuricaemia, cerebrovascular disease, cardiovascular disease, respiratory disease and malignancy were prevalent in male participants.

**Factors associated with SRH and life satisfaction**

**Table 2** presents the results of the univariate and multivariate logistic regression analyses. IADL, frailty, depression and multimorbidity were associated with poor SRH in both the unadjusted and adjusted models. As the
number of co-occurring chronic conditions increased, subjective health tended to be impaired and having six or more conditions was statistically significantly associated with poor SRH even after adjustment for other variables including depression. When the number of co-occurring conditions was six, compared with zero or one, the OR for impaired SRH was 4.80 (95% CI 1.34 to 17.11, p=0.016) in the adjusted model.

High BMI, smoking and frailty were associated with low SWLS in the unadjusted model, but the association disappeared in the adjusted model. No association was observed between multimorbidity and low SWLS, even in the presence of nine or more conditions. Only depression was associated with low SWLS in the adjusted model.

**Type of conditions and subjective health outcomes**

Table 3 shows the association of each condition with subjective health outcomes. Cerebrovascular disease, heart disease, respiratory disease, connective tissue disease and arthritis showed significant associations with poor SRH after adjustment. Connective tissue disease had the highest OR (OR 3.21; 95% CI 1.19 to 8.66, p=0.021), followed by cerebrovascular disease (OR 2.68; 95% CI 1.51 to 4.78, p<0.001). Most of the conditions were not associated with low SWLS, but arthritis exhibited a statistically significant association (OR 1.92; 95% CI 1.32 to 2.78; p<0.001 in the adjusted model).

**DISCUSSION**

With the ageing global population, the prevalence of multimorbidity has increased in various countries. Although the prevalence varies by definition of multimorbidity, previous studies have demonstrated that the prevalence of multimorbidity increases with age and is reported to be nearly 100% among patients aged ≥85 years. This study revealed that multimorbidity is very common even in a population of physically independent very old community-dwelling persons. The presence of six or more conditions was associated with poor SRH in this population, and the odds increased with the number of conditions. Multimorbidity has been defined by WHO as the presence of two or more chronic health conditions. Since multimorbidity is the norm among the very old persons, our results suggest that those who have six or more chronic conditions need to be monitored closely in clinical settings, particularly with regard to poor subjective health.

Our findings are consistent with those of past studies reporting that depression impairs subjective health.
Table 2  OR of baseline characteristics on poor self-rated health and low life satisfaction

<table>
<thead>
<tr>
<th></th>
<th>Poor Self-rated health</th>
<th></th>
<th>Low life satisfaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>P value</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Age</td>
<td>0.93 (0.81 to 1.06)</td>
<td>0.88 (0.76 to 1.03)</td>
<td>0.118</td>
<td>0.95 (0.84 to 1.08)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.73 (0.51 to 1.04)</td>
<td>0.73 (0.47 to 1.13)</td>
<td>0.155</td>
<td>0.89 (0.64 to 1.24)</td>
</tr>
<tr>
<td>BMI &gt;18.5</td>
<td>0.98 (0.47 to 2.06)</td>
<td>0.964</td>
<td>0.582</td>
<td>0.77 (0.36 to 1.64)</td>
</tr>
<tr>
<td>18–25</td>
<td>Reference</td>
<td>Reference</td>
<td>0.73 (0.45 to 1.18)</td>
<td>0.60 (0.39 to 0.91)</td>
</tr>
<tr>
<td>Current drinking</td>
<td>0.88 (0.61 to 1.27)</td>
<td>0.489</td>
<td>1.05 (0.68 to 1.64)</td>
<td>0.811</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.25 (0.54 to 2.88)</td>
<td>0.595</td>
<td>0.88 (0.33 to 2.39)</td>
<td>0.808</td>
</tr>
<tr>
<td>Education (&lt;12 years)</td>
<td>1.18 (0.82 to 1.68)</td>
<td>0.375</td>
<td>1.29 (0.84 to 1.98)</td>
<td>0.243</td>
</tr>
<tr>
<td>IADL (dependent)</td>
<td>2.13 (1.36 to 3.32)</td>
<td>0.001</td>
<td>1.83 (1.09 to 3.08)</td>
<td>0.023</td>
</tr>
<tr>
<td>Frailty</td>
<td>Robust</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>1.07 (0.63 to 1.82)</td>
<td>0.799</td>
<td>1.05 (0.60 to 1.87)</td>
<td>0.856</td>
</tr>
<tr>
<td></td>
<td>2.16 (1.15 to 4.04)</td>
<td>0.016</td>
<td>1.57 (0.77 to 3.19)</td>
<td>0.215</td>
</tr>
<tr>
<td>GDS</td>
<td>0–4</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>2.66 (1.80 to 3.93)</td>
<td>&lt;0.001</td>
<td>2.41 (1.55 to 3.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>6.57 (3.30 to 13.06)</td>
<td>&lt;0.001</td>
<td>6.90 (2.97 to 16.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No of chronic conditions</td>
<td>0–1</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.36 (0.08 to 1.69)</td>
<td>0.197</td>
<td>0.53 (0.10 to 2.85)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.94 (0.29 to 3.06)</td>
<td>0.923</td>
<td>1.53 (0.40 to 5.80)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.23 (0.39 to 3.84)</td>
<td>0.725</td>
<td>1.49 (0.40 to 5.59)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.91 (0.64 to 5.71)</td>
<td>0.248</td>
<td>2.45 (0.69 to 8.73)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3.30 (1.10 to 9.88)</td>
<td>0.033</td>
<td>4.80 (1.34 to 17.11)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4.82 (1.59 to 14.64)</td>
<td>0.006</td>
<td>6.42 (1.76 to 23.33)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6.82 (1.98 to 23.51)</td>
<td>0.002</td>
<td>10.68 (2.58 to 44.26)</td>
</tr>
</tbody>
</table>

Continued
It has been reported that depressive symptoms are associated with an increase in the number of comorbidities. Depression is also known to increase non-suicidal mortality in the old population, so it is important to evaluate the presence of depression when treating patients with multimorbidity. In our study, multimorbidity was associated with poor SRH, independent of depression, frailty and IADL. This suggests that multimorbidity affects subjective health not only via depression or physical disability but via its own pathogenesis. In the patient-centred clinical method model, patient perception of a health issue is described as ‘illness’, and perception of ‘health’ is described as the patients’ ability to realise aspirations and purpose in their lives. It is not clear whether each condition causes symptoms or disability and impairs health. The combination of multiple chronic conditions affects patients’ health in a complicated manner by affecting patients’ perception of chronic condition complex and their life purpose. To understand this complexity, social and spiritual aspects need to be considered in multimorbidity research.

This study did not show an association between multimorbidity and life satisfaction. There are several

<table>
<thead>
<tr>
<th>Poor Self-rated health</th>
<th>Low life satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI) P value</strong></td>
<td><strong>OR (95% CI) P value</strong></td>
</tr>
<tr>
<td>9 or more</td>
<td>16.25 (4.38 to 60.24)</td>
</tr>
</tbody>
</table>

BMI, body mass index; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living.

Table 3 Effect of each chronic condition on poor self-rated health and low life satisfaction

<table>
<thead>
<tr>
<th>Poor self-rated health</th>
<th>Low life satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI) P value</strong></td>
<td><strong>OR (95% CI) P value</strong></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.47 (0.99 to 2.16)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.39 (0.86 to 2.25)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1.63 (1.15 to 2.33)</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>2.07 (1.25 to 3.43)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3.42 (2.17 to 5.39)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>3.03 (0.27 to 33.65)</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.58 (0.13 to 2.49)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2.00 (1.38 to 2.90)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>2.35 (1.63 to 3.39)</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>1.72 (1.17 to 2.53)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.96 (1.17 to 3.27)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1.94 (0.90 to 4.20)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>2.88 (1.33 to 6.21)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.53 (1.02 to 2.28)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2.41 (1.68 to 3.46)</td>
</tr>
<tr>
<td>Eye disease</td>
<td>1.35 (0.87 to 2.10)</td>
</tr>
<tr>
<td>Prostate disease</td>
<td>1.43 (0.96 to 2.14)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.48 (0.98 to 2.23)</td>
</tr>
</tbody>
</table>

The adjusted models include age, sex, current drinking, current smoking, BMI, IADL, education (high school graduation or higher), frailty and depression.

BMI, body mass index; IADL, instrumental activities of daily living.
explanations for this. For example, one of the items in the SWLS involves an implicit reference to the past, meaning it might be a long-term psychometric data. Older people who were satisfied with their lives when they were young may score high on the SWLS even if they were not satisfied with their current state with multimorbidity. The SWLS has been validated in many countries, but some components of the SWLS vary across countries. For instance, Asian people tend to value social connections rather than individual achievement. In this study, social connection or social participation was not considered, which might have masked the impact of multimorbidity on life satisfaction. Furthermore, the impact of multimorbidity on life satisfaction is reported to be small in older adults with independent ADLs. Longitudinal follow-up surveys of this cohort are needed to address the potential effects of disability on life satisfaction, as our participants become older and frail.

In the condition-specific analysis, we found a correlation with poor SRH in conditions that are likely to cause symptoms and functional limitations in daily life. Cerebrovascular disease, heart disease and arthritis are associated with mobility limitation and are subsequently linked to long-term care dependency. Respiratory diseases such as chronic obstructive pulmonary disease are typical chronic symptomatic conditions in the very old persons. Dementia tended to be associated with poor SRH, but the correlation was not statistically significant. This could result from the small number of participants with dementia in our cohort, but previous studies in patients with dementia have also shown an inconsistent association between SRH and mortality. Studies investigating the structure of SRH in the very old persons have shown that the influence of disease on SRH differs with the existence of dementia. Because patients with dementia may have a different awareness of their condition, the impact of multimorbidity on subjective health and wellbeing could be different. Future studies with people with various degree of dementia and cognitive impairment are warranted to examine the actual association between multimorbidity and SRH.

**Study limitations**

Due to the nature of the cross-sectional study, inferences could not be determined on the causality of the relationship. Although we obtained medical history via physician-led interviews, the accuracy might have been limited because this strategy depends on the participant’s memory. The accuracy could be improved with the use of information regarding the number of conditions by referring to medical records and medical claim data. The prevalence of dementia and disability was relatively low in this study because we enrolled community-dwelling and physically independent people. Thus, the generalisability of our findings is limited. The strength of this study is that we included a relatively large sample size of very old persons aged ≥85 years. Our comprehensive assessment allowed us to examine the associations between multimorbidity and subjective health adjusted for a spectrum of coexisting conditions from frailty and physical function to depression. Future studies involving follow-up of this cohort will allow a comparison of the predictive power of multimorbidity, frailty and depression for predicting incident disability and mortality.

Several studies have reported different effects of subjective health perception and mortality in males and females. It has been reported that females tend to estimate their own health lower than males, and males tend to place more emphasis on physical functioning. In our study, there was no difference in subjective health perceptions between the sexes, but some conditions may influence subjective health perceptions differently in males and females. Further research is needed to reveal the process by which each condition affects subjective health perception and mortality in males and females.

In conclusion, our results demonstrate that multimorbidity, defined as having two or more chronic conditions, is prevalent (94.7%) in the independent, very old community-dwelling persons. Multimorbidity was associated with poor SRH when six or more conditions were present, and stroke and arthritis may have strong impacts. Our study contributes to the current knowledge of the psychometric impact of multimorbidity in the very old persons, whose primary care physicians are expected to play an increasingly important role in the maintenance of health and well-being.

**Author affiliations**

1. Center for General Medicine Education, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
2. Department of Neurology, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
3. Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan
4. Center for Supercentenarian Medical Research, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan
5. Faculty of Science and Technology, Keio University, Yokohama, Kanagawa, Japan
6. Graduate School of System Design and Management, Keio University, Yokohama, Kanagawa, Japan
7. Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan

**Presented at**


**Acknowledgements**

We thank the study participants of the KAWP, the Kawasaki Municipality, and Ms. Izumi Tamaki and Ms. Kyoko Furuta for their assistance in the recruitment of participants.

**Contributors**

All the authors conceived the study design and participated in the data interpretation. YN, TH, YAb, MT and YAr participated in the data collection. TA, YAb, SF and YAr participated in the data analysis. TA performed the final statistical analysis. YAb assisted in the preparation of the data. TA and YAr drafted the report. TM, SF and TT provided critical revision of the draft. YAr is responsible for the overall content as guarantor. All authors approved the final version of the report.

Funding This study was supported by a Grant-in-Aid for Scientific Research (No: 18H03055) from the Japan Society for the Promotion of Science, JST Research Complex Programme (JP15667051), AMED under Grant Number (JP20im0210051h0004), and a grant from the Kelo Global Research Institute (no grant number) and the Kanagawa Institute of Industrial Science and Technology (KISTEC, no grant number).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study is approved by the ethics committee of Keio University School of Medicine. (Study ID: 20160209).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets analysed in the current study will be available on request with an appropriate research arrangement with approval of the research ethics committee of Keio University School of Medicine for Clinical Research.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is not-commercial and/or omissions arising from translation and adaptation or otherwise.

ORCID iD Yasumichi Arai http://orcid.org/0000-0003-1746-965X

REFERENCES


