Complex multimorbidity and mortality in Japan: a prospective propensity-matched cohort study

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ABSTRACT

Objectives There are limitations to defining multimorbidity (MM) based on a simple count of diseases. To address these limitations, the concept of complex MM (CMM) focuses on how many body systems are affected in a single patient, rather than counting comorbid conditions. This study compared the prediction of mortality among older Japanese adults between CMM and conventional MM.

Design A population-based prospective cohort study.

Setting The Japan Gerontological Evaluation Study, a nationwide longitudinal cohort study, which ran from 2010 to 2016.

Participants Functionally independent individuals who were older than 65 and had complete illness data at the time of baseline survey were eligible.

Outcomes measure CMM was defined as the coexistence of 3 or more body system disorders at baseline. We calculated the propensity for each individual to develop CMM based on a wide array of characteristics, including socioeconomic status and health behaviours. Individuals with and without CMM were then matched on their propensity scores before we estimated overall survival using a log-rank test.

Results Our 6-year follow-up included 38 889 older adults: 20 233 (52.0%) and 7565 (19.5%) adults with MM and CMM, respectively. In the MM-matched cohort (n=15 666 pairs), the presence of MM was significantly associated with increased mortality (HR 1.07; 95% CI 1.01 to 1.14; p=0.02 by the log-rank test). A similar mortality association was found in the CMM-matched cohort (n=7524 pairs, HR, 1.07; 95% CI 0.99 to 1.16; p=0.08 by the log-rank test).

Conclusion This is the first study to report the association between CMM and mortality among older adults in Japan. MM and CMM predict mortality in older adults to a similar degree. This finding needs to be replicated with more precision in larger samples.

INTRODUCTION

There are limitations in defining multimorbidity (MM; the co-occurrence of diseases in the same person) based on a simple count of diseases, and a new concept of ‘complex MM’ (CMM) has thus been proposed. CMM focuses on the impact across the different body systems rather than counting comorbid conditions.

In CMM, diseases are categorised by the body system they affect. Because impairments of the same body system often have similar interventions, their impacts on patient prognosis are expected to be similar. Therefore, it makes biological sense to combine closely related diseases (eg, osteoporosis and fractures) as affecting a single body system (ie, musculoskeletal and connective disorders) rather than counting them as two separate diseases when evaluating the impact of multiple comorbid conditions. In turn, disorders of different body systems should be counted separately because they need more complex and extensive treatment, and the treatment of one disease may adversely affect another. Furthermore, from a methodological perspective, focusing on body system disorders may be more reliable method for collecting patient self-report data as patients are apt to misclassify individual conditions (eg, osteoarthritis vs rheumatoid arthritis or asthma vs COPD (chronic obstructive pulmonary disease)) but they are unlikely to mistake the affected body system. CMM is also likely to be a more reliable method as it may avoid issues of whether a clinician sees two very similar diseases as distinct and thereby avoids the issue of some clinicians recording a single condition while others record two.
A growing number of studies have demonstrated the negative impact of MM on patient outcomes, showing that MM is associated with mortality, reduced quality of life, lower physical functioning and so on.\textsuperscript{1,3-6} In many reports claiming these associations, researchers have attempted to weight diseases according to severity. Although the MM approach is better than conventional medical care that tends to focus on a single disease at a time, the new concept of CMM that focuses on multiple body system disorders is expected to result in stronger predictions of patient outcomes.

There is little evidence on the impact of CMM on mortality.\textsuperscript{7} Although functional disability is associated with mortality, no previous studies have evaluated the impact of CMM by considering baseline activities of daily living status. Furthermore, previous reports that include both MM and CMM mainly performed descriptive statistics, not inferential statistics.\textsuperscript{8-11} Against this background, we used CMM and conventional MM to compare the predictions of mortality among older Japanese adults.

**METHODS**

**Data sources**

We conducted this study using the longitudinal nationwide cohort data from the Japan Gerontological Evaluation Study (JAGES),\textsuperscript{12} which was established in 2010. This study focuses on adults in Japan over 65 years of age and aims to establish a society of healthy longevity.

**Study population**

Self-administered questionnaires for the baseline survey were mailed to 95 827 older adults in Japan between August 2010 and January 2012. Adults were sampled from 13 municipalities in 7 of the 47 prefectures in Japan. All adults were functionally independent, which was defined as not receiving public long-term care (LTC) insurance. The municipalities were from three of the four major islands of Japan (Hokkaido, Honshu, Kyushu).

Among the target population, 62 426 individuals responded to the survey (response rate, 65.1%). We included individuals who were functionally independent and not receiving any nursing care or home care assistance to avoid reverse causality between MM and functional disability, which is a key factor in mortality. We included individuals who had valid ID, sex, and age information, and who were linked to LTC insurance certification registers. We excluded individuals whose functional disability status at baseline was unknown, or who were already receiving nursing care or home care assistance, or whose data on the history of present illness was missing. Finally, we identified a cohort of 38 889 individuals. Further details of the cohort flow diagram are shown in figure 1.
| Characteristic                        | With MM | Without MM | With CMM | Without CMM |
|--------------------------------------|---------|------------|----------|-------------|
| Sample size                          | 20 233  | 18 656     | 7565     | 31 324      |
| Age                                  |         |            |          |             |
| 65–69                                | 4087    | 5328       | 1205     | 8210        |
| 70–74                                | 5673    | 5745       | 1955     | 9463        |
| 75–79                                | 5413    | 4134       | 2162     | 7385        |
| 80–84                                | 3418    | 2352       | 1485     | 4285        |
| 85–89                                | 1322    | 870        | 605      | 1587        |
| 90+                                  | 320     | 227        | 153      | 394         |
| Missing                              | 0       | 0          | 0        | 0           |
| Sex                                  |         |            |          |             |
| Male                                 | 8803    | 9038       | 3051     | 14 790      |
| Female                               | 11 430  | 9618       | 4514     | 16 534      |
| Missing                              | 0       | 0          | 0        | 0           |
| No of natural teeth                  |         |            |          |             |
| 20 or more                           | 5979    | 6313       | 2020     | 10 272      |
| 10–19                                | 4946    | 4686       | 1807     | 7825        |
| 1–9                                  | 5478    | 4582       | 2170     | 7890        |
| No natural teeth                     | 3174    | 2484       | 1311     | 4347        |
| Missing                              | 656     | 591        | 257      | 990         |
| Formal education years               |         |            |          |             |
| Less than 6 years                    | 582     | 412        | 296      | 698         |
| 6–9 years                            | 9812    | 8297       | 3818     | 14 291      |
| 10–12 years                          | 6234    | 6250       | 2247     | 10 237      |
| 13 years or more                     | 3091    | 3208       | 997      | 5302        |
| Other                                | 125     | 122        | 52       | 195         |
| Missing                              | 389     | 367        | 155      | 601         |
| Marital status                       |         |            |          |             |
| Married                              | 13 555  | 13 328     | 4772     | 22 111      |
| Widowed                              | 5124    | 3944       | 2171     | 6897        |
| Divorced                             | 652     | 594        | 255      | 991         |
| Never married                        | 413     | 331        | 157      | 587         |
| Other                                | 108     | 107        | 48       | 167         |
| Missing                              | 381     | 352        | 162      | 571         |
| Living arrangement                   |         |            |          |             |
| Live alone                           | 17 195  | 16 169     | 6300     | 27 064      |
| Not alone                            | 2730    | 2138       | 1159     | 3709        |
| Missing                              | 308     | 349        | 106      | 551         |
| Financial insecurity (worries about unexpected expenses) | | | | |
| None at all                          | 1858    | 2018       | 608      | 3268        |
| Slight                               | 8218    | 8357       | 2817     | 13 758      |
| Moderate                             | 5556    | 4701       | 2144     | 8113        |
| Severe                               | 3431    | 2494       | 1554     | 4371        |
| Missing                              | 1170    | 1086       | 442      | 1814        |

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At baseline, 19 diseases were surveyed in the JAGES. Among them, as noted in table 1, we analysed the following 17 diseases to calculate MM and CMM: heart disease (including arrhythmia), stroke, high blood pressure, diabetes (including mild type), obesity, dyslipidaemia, impaired vision, gastrointestinal disease, liver disease, impaired hearing, mental disease, sleep problems, osteoporosis, joint disease/neuralgia, injury/fracture, cancer and respiratory disease. The remaining two symptoms, difficulty swallowing and difficulty with bowel movements, were excluded from the disease list in this study because they have aspects of dysfunction not disease. The JAGES did not survey diseases of the nervous system.

MM was defined as having two or more of the aforementioned diseases concurrently. For CMM, the diseases surveyed were categorised according to the body system they affected. For example, heart disease and diabetes were individually categorised into disorders of the circulatory system and endocrine system. Next, CMM was defined as the coexistence of 3+ body system disorders at baseline (see table 1).

Outcome
The outcome of this study was the 6-year incidence of mortality. We ascertained vital status from 2010 to 2016 by linking the cohort participants to the mortality records of the national LTC insurance database (follow-up rate=96.2%). The mean follow-up period was 5.6 years, and we observed 5183 (13.3%) deaths during the period.

Table 2

| Characteristic                     | With MM | Without MM | With CMM | Without CMM |
|-----------------------------------|---------|------------|----------|-------------|
| No                                | 19 191  | 17 779     | 7162     | 29 808      |
| Yes                               | 277     | 209        | 109      | 377         |
| Missing                           | 765     | 668        | 294      | 1139        |

Current employment status

| Has a paid job                    | 3259    | 4055       | 952      | 6362        |
| Retired                           | 11 344  | 10 040     | 4315     | 17 069      |
| Never had a job                   | 2623    | 2043       | 1125     | 3541        |
| Missing                           | 3007    | 2518       | 1173     | 4352        |

Alcohol consumption

| Yes                               | 5640    | 6164       | 1868     | 9936        |
| Used to drink                     | 840     | 628        | 354      | 1114        |
| No                                | 12 498  | 10 733     | 4844     | 18 387      |
| Missing                           | 1255    | 1131       | 499      | 1887        |

Smoking status

| Never smoked                      | 10 990  | 9842       | 4195     | 16 637      |
| Stopped smoking 5 or more years ago | 4499   | 4086       | 1609     | 6976        |
| Stopped smoking within the past 4 years | 913   | 899        | 334      | 1478        |
| Current smoker                    | 1632    | 1918       | 546      | 3004        |
| Missing                           | 2199    | 1911       | 881      | 3229        |

CMM, complex multimorbidity; MM, multimorbidity

Statistical analysis

Estimation of missing data

Given that the missing data was missing at random, we conducted multiple imputations using a bootstrapping Expectation-Maximisation algorithm. We analysed 20 multiply imputed datasets, taking the low missing rate of the cohort (approximately 5%) into consideration. Lastly, we combined all estimators by Rubin’s rule.

Propensity score matching

We used propensity score matching to compare overall survival among individuals with and without MM/CMM. To address potential confounding bias, we conducted propensity score matching within a logistic regression framework. The participant information included in estimating the propensity score consisted of 44 variables: age, sex, smoking status, alcohol consumption, marital status, pension, dental health, employment status, consumption of meat/fish/fruits or vegetable, education, city code and so on (see online supplemental table S1).

We performed a 1:1 matching between individuals with and without MM/CMM using the nearest-neighbour
| Characteristic                          | MM SMD in multiply imputed data | MM SMD in matching data | CMM SMD in multiply imputed data | CMM SMD in matching data |
|----------------------------------------|---------------------------------|-------------------------|----------------------------------|-------------------------|
| Age                                    | 0.24                            | 0.002                   | 0.327                            | 0.025                   |
| Sex                                    | 0.099                           | 0.001                   | 0.139                            | 0.004                   |
| Previous health check-up               | 0.01                            | 0.015                   | 0.02                             | 0.005                   |
| No of natural teeth                    | 0.11                            | 0.019                   | 0.16                             | 0.005                   |
| Consumption of meat and fish           | 0.009                           | 0.017                   | 0.017                            | 0.016                   |
| Consumption of fruits and vegetables   | 0.003                           | 0.006                   | 0.035                            | 0.012                   |
| Formal educational years               | 0.093                           | 0.045                   | 0.151                            | 0.004                   |
| Marital status                         | 0.072                           | 0.015                   | 0.118                            | 0.002                   |
| Living arrangement                     | 0.06                            | 0.033                   | 0.1                              | 0.011                   |
| Residence type                         | 0.025                           | 0.055                   | 0.058                            | 0.008                   |
| Architectural type of home             | 0.005                           | 0.086                   | 0.02                             | 0.006                   |
| Financial insecurity                   | 0.123                           | 0.004                   | 0.21                             | 0.012                   |
| Receiving pension                      | 0.023                           | 0.022                   | 0.022                            | 0.006                   |
| Current working status                 | 0.147                           | 0.002                   | 0.225                            | 0.004                   |
| Eats meals alone                       | 0.089                           | 0.02                    | 0.17                             | 0.014                   |
| Alcohol consumption                    | 0.107                           | 0.015                   | 0.145                            | 0.013                   |
| Smoking status                         | 0.079                           | 0.014                   | 0.098                            | 0.016                   |
| Falls                                  | 0.223                           | 0.004                   | 0.307                            | 0.013                   |
| Worries about falls                    | 0.266                           | 0.001                   | 0.396                            | 0.005                   |
| Goes upstairs without support          | 0.265                           | 0.009                   | 0.348                            | 0.005                   |
| Gets up out of a chair without support | 0.251                           | 0.02                    | 0.343                            | 0.01                    |
| Average time to walk                   | 0.16                            | <0.001                  | 0.203                            | 0.001                   |
| Frequency of going out                 | 0.151                           | 0.015                   | 0.207                            | 0.003                   |
| Decrease in the frequency of going out | 0.243                           | 0.001                   | 0.352                            | 0.006                   |
| Engagement in leisure activities       | 0.105                           | 0.016                   | 0.145                            | 0.008                   |
| Trust in neighbours                    | 0.079                           | 0.027                   | 0.135                            | 0.009                   |
| Support from neighbours                | 0.074                           | 0.015                   | 0.109                            | 0.002                   |
| Attachment to residence                | 0.053                           | 0.036                   | 0.086                            | 0.002                   |
| Contribution to residence              | 0.095                           | 0.009                   | 0.129                            | 0.007                   |
| Uneasiness about safety in residence   | 0.073                           | 0.011                   | 0.105                            | 0.01                    |
| Participation in local events          | 0.085                           | 0.009                   | 0.114                            | 0.008                   |
| Interactions with neighbourhood        | 0.02                            | 0.031                   | 0.049                            | 0.007                   |
| Residential environment:               |                                 |                         |                                  |                         |
| Presence of graffiti or garbage        | 0.009                           | 0.02                    | 0.019                            | 0.014                   |
| Parks or footpaths                     | 0.059                           | 0.045                   | 0.097                            | <0.001                  |
| Locations difficult for walking        | 0.076                           | 0.012                   | 0.132                            | 0.007                   |
| Risky roads or crossroads for traffic accidents | 0.044                           | 0.005                   | 0.061                            | 0.002                   |

Continued
method within a calliper (0.2 of the SD of the logit of the propensity score).\textsuperscript{17,18} We evaluated the covariate balance after matching using standardised differences. An absolute standardised difference of less than 0.1 was considered negligible in the groups (see tables 2 and 3).

**Survival data analysis**

We estimated the overall survival using Kaplan-Meier curves.\textsuperscript{18} We also compared overall survival between matched with and without MM/CMM groups using a log-rank test.

**Sensitivity analysis**

While the definition of MM we adopted in this study is one of the most commonly used definitions in previous studies,\textsuperscript{2} we analysed this cohort data with a more sensitive approach. Specifically, we analysed the association between the number of diseases or body system disorders and the mortality by multivariate analysis with the covariates used in the propensity score calculation. The results of this analysis did not change the direction or significance of the MM/CMM effect (data not shown).

We used R software packages (V.4.0.1) for all statistical analyses, and the statistical significance level was 0.05 for all analyses.

**Patient and public involvement**

This was a nationwide cohort study focusing on community-dwelling individuals. No patients and the public were involved in this research.

### RESULTS

**Baseline population characteristics**

Among the current cohort study, 20 233 (52.0%) participants out of 38 889 had MM and 7565 (19.5%) had CMM. Table 2 presents the demographic characteristics of the participants.

| Aesthetic views or buildings | MM SMD in multiply imputed data | MM SMD in matching data | CMM SMD in multiply imputed data | CMM SMD in matching data |
|-----------------------------|---------------------------------|-------------------------|---------------------------------|-------------------------|
| Shops selling fresh fruits and vegetables | 0.074 | 0.023 | 0.091 | 0.001 |
| Dangerous place to walk alone at night | 0.013 | 0.019 | 0.016 | <0.001 |
| Comfortable house or facilities | 0.066 | 0.024 | 0.107 | 0.011 |
| Someone who listens to your concerns | 0.019 | 0.01 | 0.075 | 0.007 |
| Someone to provide care in case of illness | 0.049 | 0.023 | 0.094 | 0.026 |
| Sports group or club | 0.063 | 0.008 | 0.117 | 0.031 |
| Leisure activity group | 0.06 | 0.006 | 0.088 | 0.007 |

CMM, complex multimorbidity; MM, multimorbidity; SMD, standardised mean difference

Table 3 Continued

![Figure 2](image)

**Figure 2** Kaplan-Meier curve for overall survival comparing patients with and without MM. MM, multimorbidity.

![Figure 3](image)

**Figure 3** Kaplan-Meier curve for overall survival comparing patients with and without CMM. CMM, complex multimorbidity.
cohort study. Table 3 summarises the background characteristics of the participants between the two groups before and after matching. Populations with MM/CMM were more likely to be older, were more likely to have fewer teeth, and were more vulnerable to financial insecurity (worries about unexpected expenses) compared with those without MM/CMM. Furthermore, compared with populations with MM, populations with CMM were more likely to be female, to have lower education, to eat meals alone and to be unmarried.

**MM outcome**

After the 1:1 propensity score matching, 31 332 patients were recruited and evenly classified into propensity-matched MM and propensity-matched non-MM groups. The C-statistics before matching for evaluation of the discriminatory ability of the propensity score model was 0.64 (95% CI 0.63 to 0.64). The two matched cohorts were well balanced. The populations with MM had a 7% higher mortality than those without MM as shown in figure 2 (HR 1.07; 95% CI 1.01 to 1.14; p=0.02 by the log-rank test).

**CMM outcome**

After the 1:1 propensity score matching, 15 048 patients were recruited and evenly classified into propensity-matched CMM and propensity-matched non-CMM groups. The C-statistics before matching for evaluation of the discriminatory ability of the propensity score model was 0.69 (95% CI 0.68 to 0.69). The two matched cohorts were well balanced. The populations with CMM had slightly higher mortality than those without CMM as shown in figure 3 (HR 1.07; 95% CI 0.99 to 1.16; p=0.08 by the log-rank test).

**DISCUSSION**

To the best of our knowledge, this is the first study to report the association between CMM and mortality among older adults in Japan. MM and CMM predict mortality in older adults to a similar degree.

MM is both an individual and a social issue. Low socioeconomic status (SES) individuals develop MM roughly 10–15 years earlier compared with high SES individuals. Therefore, to evaluate whether the presence of MM/CMM is causally related to mortality, SES should be considered as a confounding factor. There were larger intergroup differences in baseline variables for the CMM-matched cohort compared with the MM-matched cohort. Although CMM was already known to be associated with lower SES, the current findings indicate that CMM may be more closely related to social factors than MM.

We found that the impact of MM and CMM on mortality was similar. Furthermore, CMM was marginally statistically significantly associated with mortality. This may be partly because the current study did not consider disease severity or disease status except in the baseline survey. That is, it may not sufficiently represent body system disorders in terms of the number of disease groups affected. This finding needs to be replicated with more precision in larger samples.

There are several limitations to this study. First, the self-administered questionnaire was the basis for disease information, which may have led to recall bias. This reporting error may lead to bias in either direction because its extent depends on the type of disease and age. Second, although the results are based on a nationwide cohort study, the participants were not nationally representative, and hence external generalisability is not assured. The response rate (around 65%) was comparable to that of other cohort studies for community-dwelling individuals. Third, because this study was observational, our findings cannot be interpreted as indicating causality. Nonetheless, we attempted to minimise confounding bias through the use of propensity score matching.

**CONCLUSION**

Both MM and CMM predicted future mortality among older adults in Japan. These findings indicate the importance of the interactive effects of multiple diseases.
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