BMJ open

Prospective cohort study of fever incidence and risk in elderly persons living at home

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004998
Article Type:	Research
Date Submitted by the Author:	05-Feb-2014
Complete List of Authors:	Yokobayashi, Kenichi; Hiroshima University of Medical Science, General Internal Medicine Matsushima, Masato; Jikei University School of Medicine, Division of Clinical Epidemiology Watanabe, Takamasa; Kita-adachi Seikyo Clinic, Tokyo Hokuto Health Co-operative, family medicine Fujinuma, Yasuki; Centre for Family Medicine Development, Japanese Health and Welfare Co-operative, family medicine Tazuma, Susumu; Hiroshima University of Medical Science, General Internal Medicine
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Infectious diseases, General practice / Family practice
Keywords:	Epidemiology < INFECTIOUS DISEASES, GERIATRIC MEDICINE, Respiratory infections < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine)

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

STROBE_checklist_BMJ-Open_cohort-studies.doc

Title

Prospective cohort study of fever incidence and risk in elderly persons living at home

Kenichi Yokobayashi (KY)
Assistant Professor
Department of General Internal Medicine, Hiroshima University of Medical Science, Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Masato Matsushima (MM)
Professor
Division of Clinical Epidemiology, Jikei University School of Medicine
3-25-8 Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan

Takamasa Watanabe(TW)
Director
Kita-adachi Seikyo Clinic, Tokyo Hokuto Health Co-operative
3-1-5 Iriya, Adachi-ku, Tokyo, 121-0836, Japan

Yasuki Fujinuma (YF)
Director
Centre for Family Medicine Development, Japanese Health and Welfare Co-operative Federation
3-22-1 Ukima, Kita-ku, Tokyo 115-0051, Japan

Susumu Tazuma (ST)
Professor
Department of General Internal Medicine, Hiroshima University of Medical Science,

Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Corresponding author: Kenichi Yokobayashi
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan
E-mail: yokobayashiken@gmail.com
Tel:082-257-5461 Fax: 082-257-1597

Keywords: fever, geriatrics, home care, infection, outcome

Word count: 2704 words

Abstract (289 words)

Objective: To determine the incidence of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes from a practical standpoint.

Design: Prospective cohort study.

Setting: Five clinics in downtown Tokyo that process an average of 50-200 outpatients/day.

Participants: Patients (n = 419) aged ≥65 years received home medical management from the five clinics between October 1, 2009 and September 30, 2010.

Main outcome measures: Fever (≥37.5°C or ≥1.5°C above usual body temperature), diagnosis at onset and outcomes (cure at home, hospitalization, death).

Results: The incidence of fever was 2.4/1000 patient-days (95% CI, 2.1 to 2.7). Fever occurred at least once (229 fever events) in 45.5% of the participants during the study period. Fever was more likely to arise in wheelchair-bound or bedridden than ambulatory individuals, with a risk ratio of 1.9 (hazard ratio 1.8 (95% CI 1.3 to 2.6; $P < 0.01$), in moderate-to-severe than in none-to-mild cognitive impairment (risk ratio, 1.8; hazard ratio [HR], 1.7 (95% CI 1.1 to 2.5, $P = 0.01$) and in those whose care-need levels were ≥3 than ≤2 (risk ratio, 3.4; HR, 4.2 (95% CI 2.8 to 6.3; $P < 0.01$). The causes of fever were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and the common cold (n = 13). Fever was cured in 67% and 23% of patients at home and in hospital, respectively, and 5% of patients each died at home and in hospital. Antimicrobial agents treated 153 (67%) events in the home medical care setting.

Conclusions: Fever that developed in about half of the 419 patients was more likely to

occur in those requiring higher care levels and the main cause of fever was pneumonia/bronchitis.

Article summary

Strengths and limitations of this study

- This is the first prospective, multicenter study to describe the status of fever among home-dwelling elderly.
- The present study revealed the incidence and risk factor of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes.
- Some fever occurrences might have remained undetected.

Introduction

In the face of a rapidly aging population combined with a diminishing number of children, the numbers of facilities to care for the elderly and of hospitals that can accept inpatients in Japan are inadequate[1]. The predicted death toll for 2030 is 1.6 million, but where 400,000 of these deaths will occur has not been predicted[1]. Under these conditions, the Ministry of Health, Labour and Welfare in Japan has promoted home medical care/management rather than in-hospital care[2].

In the Japanese home medical care system, physicians regularly make house calls to patients, in contrast to other countries where nurses or public healthcare professionals perform this task. Doctors regularly visit patients at home for about 20 min twice each month. Patients or their relatives can call for an emergency home visit on demand according to medical emergencies[3]. The leading objectives of medical care at home are to manage brain and nervous system disorders, such as the sequelae of cerebral infarction, Parkinson's disease and dementia, followed by those with cardiovascular disorders, respiratory disorders and malignant neoplasms[3].

Among the elderly receiving home medical care, the major issues comprise fever and infection that impose heavy burdens on not only patients and their relatives, but also medical professionals, since events related to fever reportedly account for many nighttime home visits in Japan[4]. However, because healthcare providers are not always available to patients at home, unlike those in nursing homes[2], the actual incidence and frequency of infection can be difficult to ascertain. Thus, the incidence, risk factors and causes of fever need to be determined. Although the incidence of fever should be high because immune function decreases with aging and chronic comorbidity[5], only our previous retrospective study has shown a fever incidence of

2.3/1000 patient-days among home-dwelling elderly[6]. The reported incidence of infection in nursing homes is quite similar to that in the home setting (~4.1/1000 patient-days)[7]. However, the incidence of fever per se in nursing homes has not apparently been defined. In addition, we previously found that fever was more likely to occur in individuals with high care-need levels and the three most common causes were pneumonia/bronchitis, urinary tract, and skin and soft tissue infections[6].These three causes were similar to those identified by studies at nursing homes[8-11].

However, the results of our previous retrospective cohort study at a single institution might not have been generally applicable. In addition, most information was obtained from medical records and thus the possibility cannot be ruled out that fever incidences were under-reported, and that measurements of risk factors and judgments regarding the causes of fever were inaccurate.

Thus, the present multicenter prospective cohort study aimed to determine the incidence of fever among elderly persons under home medical management, diagnosis at the time of fever onset and outcome (cure at home, hospitalization, death) from a pragmatic standpoint. Whether or not level of care-need, ADL and cognitive function can predict the onset of fever was also assessed.

Methods

Study design

Prospective cohort study.

Setting

The study was implemented at Seikyo Ukima, Kajiwara, Seikyo, Kita-adachi Seikyo and Akabanehigashi clinics that serve the 23 wards of Tokyo. All are located in

residential areas within 15 km of downtown Tokyo (Tokyo Station) and are teaching clinics for senior residency programs in family doctor training. Two to five full-time doctors at these clinics process an average of 50 to 200 outpatients per day (as of April 2012).

Participants

The participants comprised all patients aged ≥65 years who were medically managed at home by physicians at the above clinics.

Follow-up

The selected patients were followed up between October 1, 2009 and September 30, 2010. Data from patients who could not be followed up because of hospitalization, moving, entering a facility or death were censored. However, follow up was restarted from the date when individuals who were hospitalized during follow up returned to medical management at home.

End-point

The end-points were onset of fever (≥37.5°C or ≥1.5°C above the individual's normal body temperature), diagnosis at onset and outcomes of fever (cured at home, hospitalized, death). To precisely determine fever rates, the investigators measured the temperatures of the participants at least once every two weeks and questioned the patients and their families about fever occurrences during the previous two weeks.

Because the three most common causes of fever at nursing homes comprised pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection, patients with fever were diagnosed using criteria based on examples from published studies of nursing homes (Table 1)[8, 12-16]. Physicians diagnosed all other diseases.

Prediction and adjustment variables

Age, sex, level of care needed, activities of daily living (ADL), cognitive function, Charlson Comorbidity Index (CCI), and medical devices (gastric fistula, domiciliary oxygen therapy, respiratory devices) were recorded or measured.

The Japanese Long-Term Care Insurance system classifies the needs of individuals aged ≥65 years as requiring constant care due to being bedridden or having dementia, requiring some support for ADL, such as help with housework or physical help, and those who might deteriorate into a state that requires constant care, and not having either of these criteria[1, 2]. This care-need classification is linked to the amount of care service benefits. Uniform criteria are applied nationwide to make objective determinations. Mental and physical status is initially examined (certification examination) by a municipal certification examiner, and then a computer reaches a decision (primary decision) based on the primary physician's written opinion, which includes medical and nursing care judgments, ADL and cognitive function determined by the individual's regular doctor (Figure 1). A care-need certification committee comprising experienced professionals in public health, medicine and welfare reach a decision (secondary decision) based on the primary decision as well as the written opinion of the primary physician and then individuals are classified as having care-need levels from 1 to 5, support need or neither. The value for level of care-need increases as more care is needed, such as that for bedridden patients or those with dementia. Most individuals at care-need level 5 are usually bedridden.

The influence of confounding by comorbidities was adjusted using the Charlson comorbidity index, which is a scored indicator of comorbid disease that can estimate prognosis after one year[17]. Comorbidities are assigned a predetermined score, such as

one for myocardial infarction history and dementia, two for hemiplegia and solid cancer without metastasis, and six for metastatic solid cancer. Higher total scores are associated with higher mortality one year later.

Statistical analysis

The incidence of fever is shown using the person-time method, together with 95% confidence intervals (CI).

The cumulative incidence of first fever occurrence was determined using Kaplan–Meier curves. Between-group comparisons of cumulative incidence were assessed using the log–rank test. The effects of confounding variables on the effect of care-need level, ADL, cognitive function and medical devices on fever were adjusted using Cox's proportional hazards model. Cognitive function and ADL closely correlated with level of care-need[18] and thus were separately analyzed. Model 1 was adjusted for sex, age, ADL, cognitive function, CCI and medical device (gastric fistula, domiciliary oxygen therapy, respirator). Model 2 was adjusted for sex, age, care-need level, CCI and medical device. We fit a competing-risks model that treated a first episode of fever as the event of interest and death as the competing event.

The level of significance was established at $P < 0.05$ for all tests.

As the primary objective of this study was a description of incidence, we did not perform the exact sample size calculation. The priority was the participation of multiple clinics to expand the external validity. Based on the result of our previous retrospective cohort study[6], moreover, 95% confidence interval of estimation was expected to be sufficiently narrow when including multiple institutions.

Ethical responsibilities

The Ethics Committee at Tokyo Hokuto Health Co-operative approved the present

protocol.

Results

The proportion of 419 eligible and registered participants who required support or care during the one-year study period was the same as the national average (Table 2). Since all of them were followed up until the day they were hospitalized, moved or entered a residence facility or died, the follow-up rate was 100%.

Overall, the total number of fever occurrences that occurred among 95,008 person-days was 229. Therefore, the incidence of fever was 2.4/1000 patient-days (95% CI, 2.1 to 2.7). Fever occurred at least once in 45.5% of the patients over the study period of one year (Figure 2A).

Figure 2B compares the cumulative incidence rates of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants. Fever was significantly more likely to occur in wheelchair-bound or bedridden, than ambulatory individuals (risk ratio: 1.9). After adjustments for sex, age, cognitive function, CCI and medical device (gastric fistula, domiciliary oxygen therapy, respirator) using the Cox proportional hazards model, the hazard ratio for wheelchair-bound or bedridden and ambulatory participants was 1.8 (95% CI 1.4 to 2.6, $P < 0.01$; Table 3 model 1).

Figure 2C compares the cumulative incidence for the first onset of fever between individuals with moderate-severe (IIa-M) and none-mild (0- I) cognitive impairment. Fever was significantly more likely to occur in those with moderate-to-severe, than with none-to-mild cognitive impairment (risk ratio, 1.8). After adjustments for sex, age, ADL, CCI and medical devices using the Cox proportional hazards model, the hazard ratio for moderate-severe and none-mild cognitive impairment was 1.7 (95% CI 1.1 to 2.5, $P =$

0.01; Table 3 model 1).

Figure 2D compares the cumulative incidence of the first onset of fever between individuals with care-need levels ≤2 and ≥3. Fever was significantly more likely to occur in those with care-need levels ≥3 than ≤2 (risk ratio, 3.4). After adjustment for sex, age, CCI and medical device using the Cox proportional hazards model, the hazard ratio [HR] for ≥3 and ≤2 was 4.2 (95% CI, 2.8 to 6.3, $P < 0.01$; Table 3 model 2).

The leading causes among all 229 fever events were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and common cold (n = 13). The fever outcomes comprised cure at home (67%) or at hospital (23%) and death at home (5%) or in hospital (5%). Of the 229 events, 153 (67%) were treated in the home medical care setting using antimicrobial agents.

Discussion

This multicenter prospective cohort study revealed an incidence of fever among home-dwelling elderly of 2.4/1000 patient-days, and about 50% of fevers occurred during a period of one year. Fever was more likely to occur among patients with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. The conditions most likely to cause fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. These issues have only been investigated until now in a single-institution retrospective cohort study[6].

Strength and weaknesses of the study

The main strength of the present study is that it is the first prospective, multicenter effort to determine the status of fever among home-dwelling elderly. Several studies outside Japan have investigated these issues in nursing homes, which are considered fairly similar to home settings. However, we previously discovered the likely incidence and risk of fever in elderly people living at home in a retrospective cohort study at a single Japanese institution[6]. The present multicenter study corrected the sample deviation associated with single facility studies. The prospective study design must have reduced underreported fever events compared with the retrospective study and ADL and cognitive functions could be determined, unlike in the retrospective study.

The retrospective cohort study showed that fever was more likely to occur in patients requiring higher care-need levels. The Japanese Long-Term Care Insurance system classifies elderly persons living at home based on ADL and cognitive function as having care-need levels of 1 to 5, support need or neither[1, 2]. These indicators of need for support and care that are equally assessed in most individuals at the start of home medical care in the Japanese medical system, appear to comprise a distinct risk factor for the subsequent occurrence of fever events, but this was only apparent in Japan. This prospective study showed that ADL and cognitive function are sufficiently adaptable to also be considered as significant risk factors for fever events outside Japan. Fever is significantly more likely to occur in wheelchair-bound or bedridden and moderate-severe cognitive impairment and thus health care providers should consider these conditions. Since elderly patients with lower ADL or cognitive function were more likely to develop pneumonia, its prevention via improving oral care or by pneumococcal vaccination should be useful for such patients.

Our retrospective study uncovered the leading causes of fever among elderly patients

under home medical care. The top three sources were pneumonia/bronchitis, urinary tract infection, and skin and soft tissue infection, as they are in nursing homes outside Japan. However, that was a retrospective cohort study at a single institution and these diagnoses was obtained from medical records, and thus judgments regarding the causes of fever might be inaccurate. The present prospective study is reliable because these three source diseases were determined based on predefined criteria using examples from published studies of nursing homes[8, 12-16] (Table 1).

Our study has some limitations. Even if the prospective study increased the frequency of fever, some occurrences might have remained undetected. Information about fever in the previous retrospective cohort study was obtained from medical records and thus fever was probably underestimated. We improved the detection rate by taking the temperatures of the patients at least once every two weeks and questioning the patients and their families about fever during the previous two-week interval. However, the incidence of fever increased only from 2.3 to 2.4. A possible reason for this is that fevers were defined as temperatures ≥37.5°C in the present study, compared with ≥37.2°C in the retrospective study. Since healthcare providers are not always at the homes of patients unlike in nursing homes and the temperatures of patients cannot be measured every day, some fevers might not have been reported to medical staff. In addition to regular temperature measurements by visiting nurses and/or trained home helpers, family members measured temperatures when they felt that the patient seemed ill. We considered that many such unreported events did not require medical services. That is, the events determined herein had been recognized by medical staff as being evident problems. Although fever might have been under-reported, we considered that

the events analyzed herein were thought to be true to the home-medical care setting.

Implications for future research

The need for home medical care will probably increase as the number of aged persons increases in many countries. Because healthcare providers are not always available on demand for those under home medical care, events such as fever might increase concerns about health for patients and their families, and the burdens on healthcare providers might increase similarly to those in nursing homes[19]. Doctors regularly attend patients at home according to the Japanese system of home medical care, whereas nurses assume this role in some other countries[20-22]. Many such nurses have undergone specialized training[21-23] and their ability to manage patients at home might be equivalent to that of doctors in Japan. However, extrapolation to other countries, or even other areas in Japan, might be difficult due to variations in social/medical circumstances. Therefore, further studies should investigate the issues addressed herein in other settings.

Conclusion

The incidence of fever among home-dwelling elderly patients was 2.4/1000 patient-days, with fever occurring in about half of the participants within a period of one year. Fever is more likely to occur among individuals with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. The top three causes of fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. The rate of pneumonia/bronchitis was particularly high. Strategies to prevent pneumonia from

arising should be targeted at home-dwelling elderly persons with low ADL and/or cognitive function.

Table 1. Diagnosis based on previously defined criteria.

Diagnosis	Criteria
Pneumonia	At least two of the following: ・Fever ・Tachypnea (respiratory rate ≥ 25/min) ・Cough ・Pleuritic chest pain ・Crackles, wheezes or bronchial breath sounds ・Decreased level of consciousness or increased confusion ・Dyspnea ・Tachycardia (pulse rate ≥ 100/min) ・New or worsening hypoxemia ($SpO_2 \leq 91\%$)
Urinary tract infection	At least three of the following without an indwelling catheter: ・Fever or chills ・New or increased burning pain on urination ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine and worsening mental function At least two of the following signs with an indwelling catheter: ・Fever or chills ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine

	• Worsening mental function
Skin and soft tissue infection	At least two of the following: • Fever • Red skin • Hot skin • Painful skin • Skin swelling • Pus discharge

Table 2. Basic attributes of participants.

Participants (n = 419)	Male (n = 166)
Mean age ± SD (years) at start of follow-up	83.4 ± 8.3
Total observation person-days	95,008
Average observation ± SD (days)	226.7 ± 134.2
Median observation (range) (days)	253 (1–365)
Activities of daily living (n)	J1-A2:185 B1-C2:234
Cognition (n)	0-I: 161 IIa-M:258
Level of care-need (n)	
Support-need to care-need level 2	189
Care-need level 3 to 5	224
Gastrostoma (n)	21
Respiratory device (n)	2
Domiciliary oxygen therapy (n)	28
Charlson Comorbidity Index ± SD	2.7 ± 2.0

Table 3. Proportional hazards model for fever.

Model 1

Variable	Hazard ratio (95%CI)	P
Age	1.02 (1.00–1.04)	0.06
Sex (F vs. M)	0.87 (0.61–1.24)	0.44
Activities of daily living (WB or bedridden vs. ambulatory)	1.81 (1.25-2.62)	<0.01
Cognition (moderate-severe vs. none-mild)	1.66 (1.12-2.47)	0.01
Gastrostoma	1.70 (0.93-3.11)	0.08
Respirator	7.00 (2.24-22.25)	<0.01
Domiciliary oxygen therapy	0.77 (0.37-1.60)	0.48
Charlson Comorbidity Index	1.10 (1.01–1.20)	0.02
WB, wheelchair-bound or bedridden vs. ambulatory.		N=419

Model 2

Variable	Hazard ratio (95%CI)	P
Age	1.03 (1.01–1.05)	<0.01
Sex (F vs. M)	0.94 (0.65–1.36)	0.76
Care-need level(≥ 3 vs. ≤ 2)	4.17 (2.76-6.29)	<0.01
Gastrostoma	1.47 (0.82-2.62)	0.19
Respirator	5.86 (2.76-12.45)	<0.01
Domiciliary oxygen therapy	0.67 (0.32-1.42)	0.30
Charlson Comorbidity Index	1.11 (1.02–1.21)	0.01
		N=413*

*Care-need levels were not determined in six participants and thus data from 413 patients were analyzed in model 2.

Acknowledgments

This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine, and won the First Prize at the Japan Primary Care Association 2nd Conference. Guidance was received from the Jikei Clinical Research Program for Primary Care at Jikei University School of Medicine. We thank all the staff at Seikyo Ukima Clinic, Kajiwara Clinic, Seikyo Clinic, Kita-adachi Seikyo Clinic and Akabanehigashi Clinic for providing valuable support.

Contributors: KY and MM contributed equally to this study. KY designed the study and participated in study implementation, data collection, data analysis and writing the manuscript. He also serves as guarantor. MM analyzed the data and drafted the manuscript. YF participated in study design, implementation, and data collection. ST participated in study design and writing the manuscript. All authors had full access to

the data and take responsibility for the integrity of the data and accuracy of the analysis. The study hypothesis arouse before inspection of the data

Funding: This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine. The study sponsor had no role in the study design, data collection, analysis and interpretation, writing the report, or the decision to submit the article for publication. All authors are independent of the funding sources.

Competing interests: None

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

Ethical approval: The Ethics Committee at Tokyo Hokuto Health Co-operative (Tokyo, Japan) approved the study (number 32/2009). Informed consent for the patients was obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

References

1) Ministry of Health, Labour and Welfare Central Social Insurance Medical Council. Available at: http://www.mhlw.go.jp/stf/shingi/2r9852000001qd1o.html.
2) Ministry of Health, Labour and Welfare. Implementation of home visit. Available at: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/zaitaku/index.html.
3) National Federation of Health Insurance Societies. Investigation research report for medical care service at home. Tokyo; 2008. p. 1-172.
4) Ishibashi R, Hayashi H, Katagiri J, Io K. For death at home. Hospice and Home Care. 2009;17(1):17-21 (in Japanese).
5) Norman DC. Fever in elderly. Clin Infect Dis. 2000;31:148-51.
6) Yokobayashi K, Matsushima M, Fujinuma Y. Retrospective cohort study of the incidence and risk of fever in elderly people living at home: A pragmatic aspect of home medical management in Japan. Geriatr Gerontol Int. 2013;13:887-93.
7) Bentley DW, Bradley S, High K. Practice guideline for evaluation of fever and infection in long-term care facilities. Clin Infect Dis. 2000;31:640-53.
8) Zimmerman S, Gruber-Baldini AL, Magaziner J. Nursing Home Facility Risk Factors for Infection and Hospitalization: Importance of Registered Nurse Turnover, Administration, and Social Factors. J Am Geriatr Soc. 2002;50:1987-95.
9) Smith PW, Bennett G, Bradley S. Infection prevention and control in the long-term care facility. Am J Infect Control. 2008;36:504-35.
10) High K, Bradley S, Gravenstein S. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities. Clin Infect Dis. 2009;48:149-71.
11) Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999;43:S9-18.
12) Guideline for The Diagnosis and Management of Nursing Home Acquired Pneumonia. Alberta Medical Association, 2008.

13) Loeb M, McGeer A, McArthur M. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999; 159(17): 2058-64.

14) Stevens DL, Bisno AL, Chambers HF. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. Clin Infect Dis. 2005;41:1373-406.

15) Kamel HK. Managing Urinary Tract Infections in the Nursing Home: Myths, Mysteries and Realities. Internet Journal of Geriatrics and Gerontology. 2004;1. DOI: 10.5580/205c.

16) Nicolle LE. Urinary tract infection in long-term–care facility residents. Clin Infect Dis. 2000;31:757-761.

17) Charlson ME, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

18) Togami J, Nakahara M. Relationship between grade of care required and activities of daily living, dementia in elderly of day rehabilitation care. Yanagawariha Fukuoka Kokusai Kiyo 2009;5:57-60.

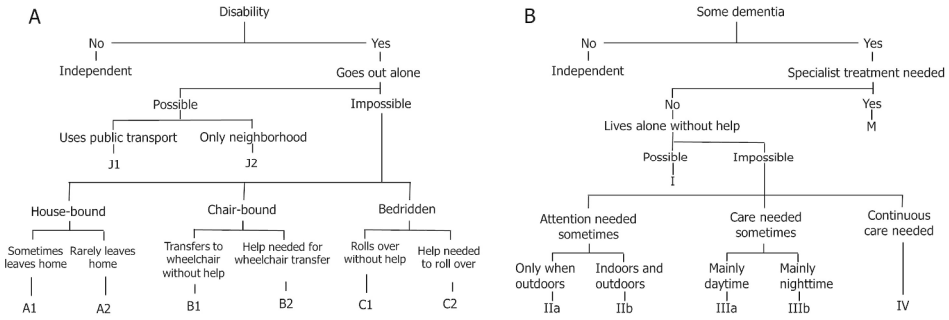
19) Leibobitz A, Baumoehl Y, Habot B, et al. Management of adverse clinical events by duty physicians in a nursing home. Aging Clinical and Experimental Research 2004;16(4):314-318.

20) Tatara R. Palliative care by primary care team. The Japanese Academy of Home Care Physicians 2009;10(2):144-151.

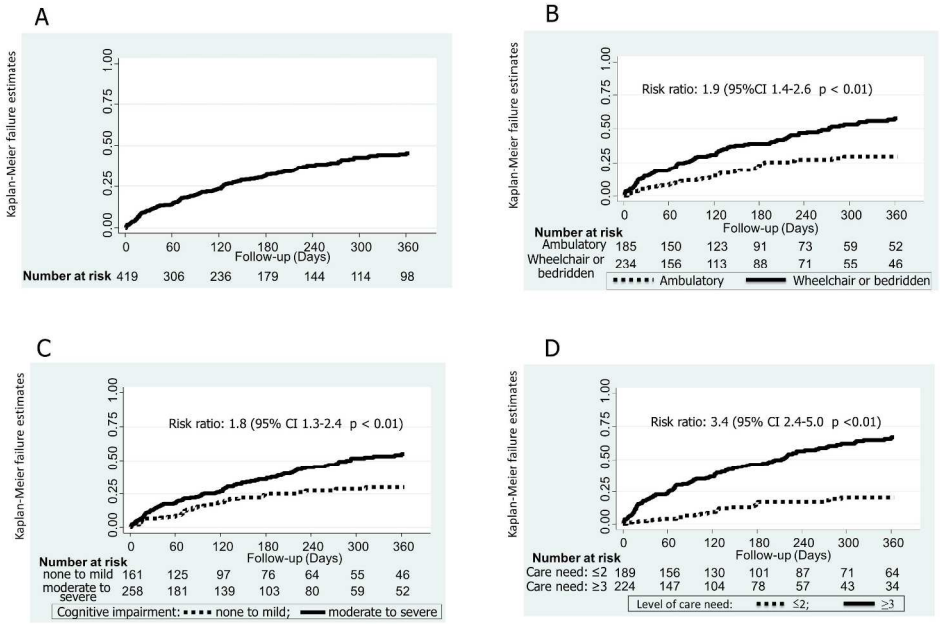
21) Katayama F. Learning from Hospice at U.S. The Japanese Academy of Home Care Physicians 2009;10(2):152-157.

22) Riwa F. Home medical and nursing care in the U.S. and England. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p. 264-284.

23) Izawa T. Home medical and nursing care at Sweden. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p. 285-305.



(A)Judgment of degree of independent daily living among disabled elderly persons. (B)Judgment of degree of independent daily living among elderly persons with dementia.
500x190mm (156 x 156 DPI)



(A)Cumulative incidence of fever. (B)Cumulative incidence of fever affecting ADL. (C)Cumulative incidence of fever in cognitively impaired. (D)Cumulative incidence of fever at different levels of care.
419x289mm (186 x 186 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	8, 10-11
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	10
		(*e*) Describe any sensitivity analyses	No sensitivity anayeses

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, 11
		(b) Give reasons for non-participation at each stage	8, 11
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19(Table 2)
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	19(Table 2)
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

研究実施計画書

研究課題

在宅高齢者の発熱実態調査

研究代表者

生協浮間診療所　横林賢一　yokobayashiken@gmail.co.jp

共同研究者

東京慈恵医科大学　松島雅人

梶原診療所　平原佐斗司、斉木啓子

生協浮間診療所　藤沼康樹、阿部佳子

北足立生協診療所　井上真智子、渡邉隆将

せいきょう診療所　安来志保

赤羽東診療所　高橋慶

１．研究計画の経緯・背景

日本において病院数が抑制され、減少しているにも関わらず高齢者数は増加し続けており[1)]、今後ますます在宅医療の必要性が増してくることが予想されるが、国内外を含め在宅医療に関する研究は少ない。在宅医療の中でも高齢患者の発熱・感染症は、症状が非典型的、コミュニケーションがとりにくい、高熱などの炎症所見が乏しい、簡単に検査を行える環境にないなどの理由のため診断・治療が困難であるが、在宅高齢患者の発熱・感染症に関する研究は報告されていない。

一方、海外の研究では在宅設定に比較的近いと思われるnursing homeに関する発熱・感染症に関する研究が複数なされている。Nursing homeにおける感染症は、4/1000 patient-daysと報告されており[2)6)]、その内訳として、肺炎･気管支炎などの下気道感染症（1.2/1000 patient-days）[3)]、尿路感染症、褥瘡感染などの皮膚・軟部組織感染症が多数を占めると報告されている[2)4)5)6)7)]。抗菌薬に関しては、nursing homeでの抗菌薬使用状況は0.46 antibiotic courses/100 patient-days（3899人のうち、1年間で抗菌薬の治療を受けた人が54%）であり、使用された抗菌薬の中ではβラクタム系抗菌薬が最多（54%）であった[8)]。抗菌薬の疾患別の内訳は、全使用抗菌薬のうち、尿路感染症が36%と最も多く（ただし9%の無症候性細菌尿を含む）、皮膚感染症、下気道感染症、上気道感染症がそれぞれ15%程であった[8)]。抗菌薬処方時の診断のための診察・検査が記録されているのは44%に留まり、設定された診断基準に合致するものは11%と低値であった[8)]。

在宅設定に比較的近いと思われる海外のnursing homeの研究はいくつかあるものの、日本の在宅医療設定における発熱・感染症の研究はこれまでなされていない。よって日本の在宅医療設定における高齢者の発熱の発生率、診断、抗菌薬使用状況、予後を調査することで、在宅医が判断に難渋する発熱・感染症の現状が明らかになり、それらを元に新たな診断・治療の方向性を見出すことができると考えられる。

２．目的

本研究は在宅医療管理中の高齢患者（65 歳以上）が発熱（37.5 度以上あるいは通常の体温より 1.5 度以上上昇した場合）を来たした際の発生率、診断、抗菌薬使用の有無、予後（在宅治癒、入院、死亡）を明らかにすることを目的とする。また、生命予後の予測因子として使用されている CCI score が発熱発生の予測因子として機能するかも検討する。初めに後向きコホート研究で 1 つの診療所の 1 年間の在宅患高齢患者の発熱・感染症の実態を調査し、後向き研究で記述されたデータから発熱発生の予測因子の吟味を行い、5 施設で 1 年間の前向きコホート研究を行う。

３．対象

後向きコホートでは、2008 年 7 月 1 日～2009 年 6 月 30 日の期間、生協浮間診療所で在宅管理を行った 65 歳以上の患者を対象とし，2009 年 6 月 30 日まで追跡する。

前向きコホートでは、2009 年 10 月 1 日～2010 年 9 月 30 日の期間、5 施設（生協浮間診療所、梶原診療所、せいきょう診療所、北足立生協診療所、赤羽東診療所）で管理を受ける 65 歳以上の在宅患者を対象とし，2010 年 9 月 30 日まで追跡する。

＜除外基準：前向き研究＞

調査への同意が得られない患者。

４．方法

＜研究デザイン＞

後向きコホート研究

前向きコホート研究

＜調査にあたっての方法：後ろ向き研究＞

（1） 対象者の抽出・同意の取得

2008 年 7 月 1 日～2009 年 6 月 30 日に生協浮間診療所において在宅管理を行った全患者を在宅患者管理台帳より抽出し対象とする。本研究は既存資料を用いる疫学研究に相当するため本人からのインフォームドコンセントの取得は必ずしも要さないと考えられる。しかし診療所またホームページには研究の概要を公開する。

（2） 基本となる臨床上の情報収集

対象者の診療録を閲覧し、年齢、性別、観察開始日、ADL（主治医意見書の障害高齢者の日常生活自立度；調査期間開始時に最も近い時期のもの)、認知度（主治医意見書の認知症高齢者の日常生活自立度；調査期間開始時に最も近い時期のもの)、介護度、CCI score（併存疾患）につき記録する。

（3） アウトカムの調査方法

対象者の診療録を閲覧し、発熱（37.5 度以上あるいは通常の体温より 1.5 度以上上昇した場合）の有無と発生日、後述する診断基準に従った診断名、抗菌薬投与の有無と経口・非経口投与の有無、発熱の予後（在宅で治癒、在宅で死亡、入院後治癒、入院後死亡、入院後不明)、死亡の有無および死亡理由につき可能な限り記録する。

（4） データの保管・解析

データ解析は、連結可能匿名化を行い、生協浮間診療所内事務室に連結表とともに厳重に保管する。匿名化されたデータは共同研究施設である東京慈恵会医科大学臨床疫学研究室にて解析が行われる。

＜調査にあたっての方法：前向き研究＞

（1） 対象者の抽出・同意の取得

調査期間中の在宅管理患者すべてを対象とする。対象者の在宅管理導入の際、担当医から研究

の目的、方法につき口頭および文書で説明のうえ、患者本人あるいは家族から同意書への署名を得る形で同意を取得する。対象者には在宅管理患者の全数調査である旨を説明する。

（2） 基本となる臨床上の情報収集

担当医による対象者の診療録閲覧および患者、家族への聴取により、年齢、性別、観察開始日、ADL（主治医意見書の障害高齢者の日常生活自立度；調査期間開始時に最も近い時期のもの）、認知度（主治医意見書の認知症高齢者の日常生活自立度；調査期間開始時に最も近い時期のもの）、介護度、在宅酸素療法の有無、人工呼吸器使用の有無、胃瘻の有無、CCI スコア（併存疾患）につき所定のフォーマットに記録する。フォーマットのコピーを 2 ヶ月に 1 度回収する。

（3） アウトカムの調査

担当医に発熱(37.5 度以上あるいは通常の体温より 1.5 度以上上昇した場合)の有無と発生日、後述する診断基準に従った診断名、抗菌薬投与の有無と経口・非経口投与の有無、発熱の転帰（在宅で治癒、在宅で死亡、入院後治癒、入院後死亡、入院後不明）につき遅滞無くカルテおよび所定のフォーマットに記載するよう説明し、2 ヶ月に 1 度データを回収する。

（4） 観察終了時の情報収集

観察終了時に、観察終了日、終了理由、死亡している場合は死因と死亡日、入院した場合は入院日と退院日、入院理由、入院後診断を記載するよう説明する。同意を取れなかった人数についても記載するよう説明する。これらの情報は観察終了日以降に回収する。

（5） データの保管・解析

データ解析は、連結可能匿名化を行い、生協浮間診療所内事務室に連結表とともに厳重に保管する。匿名化されたデータは共同研究施設である東京慈恵会医科大学臨床疫学研究室にて解析が行われる。

＜使用する調査方法・診断基準＞

（1）CCI スコア（Charlson Comorbidity Index Scoring System）

心筋梗塞、糖尿病、認知症、固形癌などの併存疾患による 1 年後の死亡率を予測する予後予測因子として世界的に広く使用されている。各々の併存疾患（全 19 疾患）は死亡リスクによって 1、2、3、6 点に割り付けられており、その合計得点が高いほど死亡率が高いとされている [9]。

（2）診断基準

発熱の原因の診断は、nursing home で多いとされる下気道感染症、尿路感染症、皮膚・軟部組織感染症については nursing home での基準を参考に下記の基準を満たすものを診断名と規定する。それ以外の診断名は主治医の判断による。

〔下気道感染症・尿路感染症・皮膚軟部組織感染症診断基準〕

- 下気道感染症・・・頻呼吸（25 回/分以上）、発熱、咳嗽、胸膜痛、呼吸音の異常（crackles, wheezes or bronchial breath sounds）、意識状態の変化、呼吸困難、頻脈（100 回/分以上）、低酸素血症（SpO2 91%以下）のうち、2 つ以上満たす場合 [2)10)]
- 尿路感染症・・・A.尿道カテーテルが挿入されていない場合、以下の 4 つのうち 3 つ以上を満たす場合;①発熱あるいは悪寒②新たな排尿時痛あるいは排尿時痛の悪化③新たな側背部あるいは恥骨上部の痛みまたは圧痛④尿の性質の変化と意識状態の悪化 [2)11)]
  B.尿道カテーテルが挿入されている場合、以下の 4 つのうち 2 つ以上を満たす場合；①発熱あるいは悪寒②新たな側背部あるいは恥骨上部の痛みまたは圧痛③尿の性質の変化④意識状態の悪化 [2)11)]
- 皮膚・軟部組織感染症・・・発熱、局所の排膿、発赤、熱感、圧痛、自発痛のうち 2 つ以上満たす場合 [2)]

＜解析＞

主要アウトカムである発熱については、person-time 法によって人・月（person-month）あたり

の発生率を算出する。また原因疾患別発熱発生率、さらに入院および死亡についても同様に発生率を求める。性、年齢、CCI score を説明変数とした Cox 比例ハザードモデルによって、発熱の発生に CCI score が予測因子となりうるかを検討する。

＜費用＞

消耗品：コピー用紙　5 万円、ファイル　3 万円、印刷トナー　２万円、USB メモリー　２万円

旅費：学会発表時およびデータ収集時　8 万円

計：20 万円

５．目標症例数

後ろ向き研究：100 人

前向き研究：350 人

６．実施場所

後向き研究：生協浮間診療所

前向き研究：生協浮間診療所、梶原診療所、せいきょう診療所、北足立診療所、赤羽東診療所

７．予想される有害事象

後向き研究：カルテ閲覧による調査であり、対象者のプライバシー保護が守られれば特に危険を伴うものではない。

前向き研究：介入を行わない調査であり、対象者への説明と参加への同意取得が公正に行われ、対象者のプライバシー保護が守られれば特に危険性を伴うものではない.

8. 緊急時の連絡先

生協浮間診療所　03-3558-8361

横林　賢一

9. 人権・プライバシーの保護について

方法の項に記載したように、後向き研究については、本研究の主旨および内容について診療所およびホームページにて公開し、研究参加を拒否できる機会を設ける。前向き研究については、対象者の在宅管理導入の際、担当医から研究の目的、方法について、また同意しなくても今後の診療に全く影響しない旨、研究結果が発表前であればいつでも同意を撤回できる旨を口頭および文書で説明のうえ、患者本人あるいは家族から同意書への署名を得る形で同意を取得する。

調査に協力・参加した患者個人の氏名は、研究結果において表現されず、個人を特定できるデータは結果には含まれない。データの集計・管理は生協浮間診療所において行い，研究代表者によって患者個人名等の個人情報はデータから分離し連結可能匿名化される。調査終了後患者個人名が特定できる調査票などはシュレッダーで破棄される。

本研究は、2009 年 7 月 9 日に王子生協病院倫理委員会にて承認を得ている。

【参考文献】

1) 総務省統計局ホームページ http://www.stat.go.jp/index.htm

2) Suzanne F. Fever and Infection in the Nursing Home. Annals of Long-Term Care 12,2004

3) Loeb M, McGeer A, McArthur M, Walter S, Simor AE. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999 Sep 27; 159(17): 2058-64.

4) Werner H . Infection in the elderly--what is different? Z Gerontol Geriatr. 2000

Oct;33(5):350-6.

5) Yoshikawa TT, Norman DC. Approach to fever and infection in the nursing home. J Am Geriatr Soc. 1996 Jan;44(1):74-82.

6) Bentley DW, Bradley S, Practice guideline for evaluation of fever and infection in long-term care facilities. J Am Geriatr Soc. 2001 Feb;49(2):210-22.

7) Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999 Dec;43 Suppl:S9-18.

8) Warren JW, Palumbo FB, Incidence and characteristics of antibiotic use in aged nursing home patients. J Am Geriatr Soc. 1991 Oct;39(10):963-72.

9) Charlson ME, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

10) Guideline for The Diagnosis and Management of Nursing Home Acquired Pneumonia. Alberta clinical practice guidelines 2008

11) Hosam K. Managing Urinary Tract Infections in the Nursing Home:Myths, Mysteries and Realities The Internet Journal of Geriatrics and Gerontology

BMJ Open

Prospective cohort study of fever incidence and risk in elderly persons living at home

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004998.R1
Article Type:	Research
Date Submitted by the Author:	04-Jun-2014
Complete List of Authors:	Yokobayashi, Kenichi; Hiroshima University of Medical Science, General Internal Medicine Matsushima, Masato; Jikei University School of Medicine, Division of Clinical Epidemiology Watanabe, Takamasa; Kita-adachi Seikyo Clinic, Tokyo Hokuto Health Co-operative, family medicine Fujinuma, Yasuki; Centre for Family Medicine Development, Japanese Health and Welfare Co-operative, family medicine Tazuma, Susumu; Hiroshima University of Medical Science, General Internal Medicine
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Infectious diseases, General practice / Family practice
Keywords:	Epidemiology < INFECTIOUS DISEASES, GERIATRIC MEDICINE, Respiratory infections < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine)

Title

Prospective cohort study of fever incidence and risk in elderly persons living at home

Kenichi Yokobayashi (KY)
Assistant Professor
Department of General Internal Medicine, Hiroshima University of Medical Science, Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Masato Matsushima (MM)
Professor
Division of Clinical Epidemiology, Jikei University School of Medicine
3-25-8 Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan

Takamasa Watanabe(TW)
Director
Kita-adachi Seikyo Clinic, Tokyo Hokuto Health Co-operative
3-1-5 Iriya, Adachi-ku, Tokyo, 121-0836, Japan

Yasuki Fujinuma (YF)
Director
Centre for Family Medicine Development, Japanese Health and Welfare Co-operative Federation
3-22-1 Ukima, Kita-ku, Tokyo 115-0051, Japan

Susumu Tazuma (ST)
Professor
Department of General Internal Medicine, Hiroshima University of Medical Science,

Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Corresponding author: Kenichi Yokobayashi
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan
E-mail: yokobayashiken@gmail.com
Tel:082-257-5461 Fax: 082-257-1597

Keywords: fever, geriatrics, home care, infection, outcome

Word count: 2909 words

Abstract (295words)

Objective: To determine the incidence of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes from a practical standpoint.

Design: Prospective cohort study.

Setting: Five clinics in downtown Tokyo that process an average of 50-200 outpatients/day.

Participants: Patients (n = 419) aged ≥65 years received home medical management from the five clinics between October 1, 2009 and September 30, 2010.

Main outcome measures: Fever (≥37.5°C or ≥1.5°C above usual body temperature), diagnosis at onset and outcomes (cure at home, hospitalization, death).

Results: The incidence of fever was 2.5/1000 patient-days (95% CI, 2.2 to 2.8). Fever occurred at least once (229 fever events) in 45.5% of the participants during the study period. Fever was more likely to arise in wheelchair-bound or bedridden than ambulatory individuals, with a risk ratio of 1.9 (hazard ratio 1.8 (95% CI 1.3 to 2.6; $P <$ 0.01), in moderate-to-severe than in none-to-mild cognitive impairment (risk ratio, 1.8; hazard ratio [HR], 1.7 (95% CI 1.1 to 2.5, $P = 0.01$) and in those whose care-need levels were ≥3 than ≤2 (risk ratio, 3.4; HR, 4.2 (95% CI 2.8 to 6.3; $P < 0.01$). The causes of fever were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and the common cold (n = 13). Fever was cured in 67% and 23% of patients at home and in hospital, respectively, and 5% of patients each died at home and in hospital. Antimicrobial agents treated 153 (67%) events in the home medical care setting.

Conclusions: Fever was more likely to occur in those requiring higher care levels and

the main cause of fever was pneumonia/bronchitis. Health care providers should consider the conditions of elderly residents with lower objective functional status.

Article summary

Strengths and limitations of this study

- This is the first prospective, multicenter study to describe the status of fever among home-dwelling elderly.
- The present study revealed the incidence and risk factor of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes.
- Some fever occurrences might have remained undetected.

Introduction

In the face of a rapidly aging population combined with a diminishing number of children, the numbers of facilities to care for the elderly and of hospitals that can accept inpatients in Japan are inadequate[1]. The predicted death toll for 2030 is 1.6 million, but where 400,000 of these deaths will occur has not been predicted[1]. Under these conditions, the Ministry of Health, Labour and Welfare in Japan has promoted home medical care/management rather than in-hospital care[2].

In the Japanese home medical care system, physicians regularly make house calls to patients. Doctors regularly visit patients at home for about 20 min twice each month. Patients or their relatives can call for an emergency home visit on demand according to medical emergencies[3]. The leading objectives of medical care at home are to manage brain and nervous system disorders, such as the sequelae of cerebral infarction, Parkinson's disease and dementia, followed by those with cardiovascular disorders, respiratory disorders and malignant neoplasms[3].

Among the elderly receiving home medical care, the major issues comprise fever and infection that impose heavy burdens on not only patients and their relatives, but also medical professionals, since events related to fever reportedly account for many nighttime home visits in Japan[4]. However, because healthcare providers are not always available to patients at home, unlike those in nursing homes[2], the actual incidence and frequency of infection can be difficult to ascertain. Thus, the incidence, risk factors and causes of fever need to be determined. Although the incidence of fever should be high because immune function decreases with aging and chronic comorbidity[5], only our previous retrospective study has shown a fever incidence of 2.3/1000 patient-days among home-dwelling elderly[6]. The reported incidence of

infection in nursing homes is quite similar to that in the home setting (~4.1/1000 patient-days)[7]. However, the incidence of fever per se in nursing homes has not apparently been defined. In addition, we previously found that fever was more likely to occur in individuals with high care-need levels and the three most common causes were pneumonia/bronchitis, urinary tract, and skin and soft tissue infections[6].These three causes were similar to those identified by studies at nursing homes[8-11].

However, the results of our previous retrospective cohort study at a single institution might not have been generally applicable. In addition, most information was obtained from medical records and thus the possibility cannot be ruled out that fever incidences were under-reported, and that measurements of risk factors and judgments regarding the causes of fever were inaccurate.

Thus, the present multicenter prospective cohort study aimed to determine the incidence of fever among elderly persons under home medical management, diagnosis at the time of fever onset and termination (cure at home, hospitalization, death) from a pragmatic standpoint. Whether or not level of care-need, ADL and cognitive function can predict the onset of fever was also assessed.

Methods

Study design

Prospective cohort study.

Setting

The study was implemented at Seikyo Ukima, Kajiwara, Seikyo, Kita-adachi Seikyo and Akabanehigashi clinics that serve the 23 wards of Tokyo. All are located in residential areas within 15 km of downtown Tokyo (Tokyo Station) and are teaching

clinics for senior residency programs in family doctor training. Two to five full-time doctors at these clinics process an average of 50 to 200 outpatients per day (as of April 2012).

Participants

The participants comprised all patients aged ≥65 years who were medically managed at home by physicians at the above 5 center clinics.

Follow-up

The selected patients were followed up between October 1, 2009 and September 30, 2010. Data from patients who could not be followed up because of hospitalization, moving, entering a facility or death were censored. However, follow up was restarted from the date when individuals who were hospitalized during follow up returned to medical management at home.

End-point

The end-points were onset of fever (≥37.5°C or ≥1.5°C above the individual's normal body temperature), diagnosis at onset and termination of fever (cured at home, hospitalized, death). To precisely determine fever rates, the investigators measured the temperatures of the participants at least once every two weeks and questioned the patients and their families about fever occurrences during the previous two weeks.

Because the three most common causes of fever at nursing homes comprised pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection, patients with fever were diagnosed using criteria based on examples from published studies of nursing homes (Table 1)[8, 12-16]. Physicians diagnosed all other diseases.

Prediction and adjustment variables

Age, sex, level of care needed, activities of daily living (ADL), cognitive function, Charlson Comorbidity Index (CCI), and medical devices (gastric fistula, domiciliary oxygen therapy, respiratory devices) were recorded or measured.

The Japanese Long-Term Care Insurance system classifies the needs of individuals aged ≥65 years as requiring constant care due to being bedridden or having dementia, requiring some support for ADL, such as help with housework or physical help, and those who might deteriorate into a state that requires constant care, and not having either of these criteria[1, 2]. This care-need classification is linked to the amount of care service benefits. Uniform criteria are applied nationwide to make objective determinations. Mental and physical status is initially examined (certification examination) by a municipal certification examiner, and then a computer reaches a decision (primary decision) based on the primary physician's written opinion, which includes medical and nursing care judgments, ADL and cognitive function determined by the individual's regular doctor (Figure 1). A care-need certification committee comprising experienced professionals in public health, medicine and welfare reach a decision (secondary decision) based on the primary decision as well as the written opinion of the primary physician and then individuals are classified as having care-need levels from 1 to 5, support need or neither. The value for level of care-need increases as more care is needed, such as that for bedridden patients or those with dementia. Most individuals at care-need level 5 are usually bedridden.

The influence of confounding by comorbidities was adjusted using the Charlson comorbidity index, which is a scored indicator of comorbid disease that can estimate prognosis after one year[17]. Comorbidities are assigned a predetermined score, such as one for myocardial infarction history and dementia, two for hemiplegia and solid cancer

without metastasis, and six for metastatic solid cancer. Higher total scores are associated with higher mortality one year later.

Statistical analysis

The incidence density of fever is shown using the person-time method, together with 95% confidence intervals (CI). This included multiple-failure events, which means all events of fever were counted over the period of home medical care. The period of hospital admission was excluded from the denominator for calculating incidence density.

In contrast, only the first episode of fever was considered in survival analyses since some participants experienced hospital admissions hampering home medical care and stayed there, which may have an effect on risk of fever after the discharge from hospital. Therefore, we did not employ multiple failure-time data in the survival analyses. Instead we treated hospital admission as well as death as competing risk event of fever in the survival analyses using competing-risk method [18].

The cumulative incidence of first fever occurrence was determined using competing-risk method. Between-group comparisons of cumulative incidence were assessed using the method developed by PePe and Mori[19].

To evaluate an independent effect of care-need level, ADL, cognitive function and medical devices on the occurrence of fever event, competing-risks regression was employed considering death and hospital admission as competing risk [20]. Cognitive function and ADL closely correlated with level of care-need [21] and thus were separately analyzed. Model 1 included sex, age, ADL, cognitive function, CCI and medical devices (gastric fistula, domiciliary oxygen therapy, and respirator). Model 2 included sex, age, care-need level, CCI and medical devices.

The level of significance was established at $P < 0.05$ for all tests.

As the primary objective of this study was a description of incidence, we did not perform the exact sample size calculation. The priority was the participation of multiple clinics to expand the external validity. Based on the result of our previous retrospective cohort study [6], moreover, 95% confidence interval of estimation was expected to be sufficiently narrow when including multiple institutions.

Statistical analyses were carried out using STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) .& 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Ethical responsibilities

The Ethics Committee at Tokyo Hokuto Health Co-operative approved the present protocol.

Results

The proportion of 419 eligible and registered participants who required support or care during the one-year study period was the same as the national average (Table 2). Since all of them were followed up until the day they were hospitalized, moved or entered a residence facility or died, the follow-up rate was 100%.

Overall, the total number of fever occurrences that occurred among 91,415 person-days was 229. Therefore, the incidence of fever was 2.5/1000 patient-days (95% CI, 2.2 to 2.8). Cumulative incidence after 1 year follow-up estimated by competing risk method was 0.37 (95%CI, 0.32 to 0.42). Fever occurred at least once among one-third of the patients over the study period of one year (Figure 2A).

Figure 2B compares the cumulative incidence function for the first onset of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants. Fever was significantly more likely to occur in wheelchair-bound or bedridden, than ambulatory individuals ($p<0.01$). After adjustments for sex, age, cognitive function, CCI and medical devices (gastric fistula, domiciliary oxygen therapy, respirator) using the competing-risks regression, the hazard ratio for wheelchair-bound or bedridden and ambulatory participants was 1.9 (95% CI 1.3 to 2.8, $P < 0.01$; Table 3 model 1).

Also, Figure 2C compares the cumulative incidence function for the first onset of fever between individuals with moderate-severe (IIa-M) and none-mild (0- I) cognitive impairment. Fever was significantly more likely to occur in those with moderate-to-severe, than with none-to-mild cognitive impairment ($p<0.01$). After adjustments for sex, age, ADL, CCI and medical devices using the competing-risks regression, the hazard ratio for moderate-severe and none-mild cognitive impairment was 1.7 (95% CI 1.1 to 2.5, $P = 0.01$; Table 3 model 1).

Figure 2D compares the cumulative incidence function for the first onset of fever between individuals with care-need levels ≤2 and ≥3. Fever was significantly more likely to occur in those with care-need levels ≥3 than ≤2 ($p<0.01$). After adjustment for sex, age, CCI and medical devices using the competing-risks regression, the hazard ratio [HR] for ≥3 and ≤2 was 4.5 (95% CI, 2.9 to 7.0, $P < 0.01$; Table 3 model 2).

The leading causes among all 229 fever events were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and common cold (n = 13). The fever outcomes comprised cure at home (67%) or at hospital (23%) and death at home (5%) or in hospital (5%). Of the 229 events, 153 (67%) were treated in the home medical care setting using antimicrobial agents.

Discussion

This multicenter prospective cohort study revealed an incidence of fever among home-dwelling elderly of 2.5/1000 patient-days, and about one-thrid of the patients experienced a fever during a period of one year. Fever was more likely to occur among patients with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. The conditions most likely to cause fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. These issues have only been investigated until now in a single-institution retrospective cohort study[6].

The retrospective cohort study showed that fever was more likely to occur in patients requiring higher care-need levels. The Japanese Long-Term Care Insurance system classifies elderly persons living at home based on ADL and cognitive function as having care-need levels of 1 to 5, support need or neither[1, 2]. These indicators of need for support and care that are equally assessed in most individuals at the start of home medical care in the Japanese medical system, appear to comprise a distinct risk factor for the subsequent occurrence of fever events, but this was only apparent in Japan. This prospective study showed that ADL and cognitive function are sufficiently adaptable to also be considered as significant risk factors for fever events outside Japan. Fever was significantly more likely to occur in wheelchair-bound or bedridden and moderate-severe cognitive impairment, which means health care providers should consider these conditions and should measure the temperatures of elderly residents with lower objective functional status more frequently. Since elderly patients with lower

ADL or cognitive function were more likely to develop pneumonia, its prevention via improving oral care or by pneumococcal vaccination should be useful for such patients.

Strengths and limitations of the study

The main strength of the present study is that it is the first prospective, multicenter effort to determine the status of fever among home-dwelling elderly. Several studies outside Japan have investigated these issues in nursing homes, which are considered fairly similar to home settings. However, we previously discovered the likely incidence and risk of fever in elderly people living at home in a retrospective cohort study at a single Japanese institution [6]. The present multicenter study corrected the sample deviation associated with single facility studies. The prospective study design must have reduced underreported fever events compared with the retrospective study and ADL and cognitive functions could be determined, unlike in the retrospective study.

Our retrospective study uncovered the leading causes of fever among elderly patients under home medical care. The top three sources were pneumonia/bronchitis, urinary tract infection, and skin and soft tissue infection, as they are in nursing homes outside Japan. However, that was a retrospective cohort study at a single institution and these diagnoses was obtained from medical records, and thus judgments regarding the causes of fever might be inaccurate. The present prospective study is reliable because these three source diseases were determined based on predefined criteria using examples from published studies of nursing homes [8, 12-16] (Table 1).

Our study has some limitations. Even if the prospective study increased the frequency of fever, some occurrences might have remained undetected. Information about fever in

the previous retrospective cohort study was obtained from medical records and thus fever was probably underestimated. We improved the detection rate by taking the temperatures of the patients at least once every two weeks and questioning the patients and their families about fever during the previous two-week interval. However, the incidence of fever increased only from 2.3 to 2.5. A possible reason for this is that fevers were defined as temperatures ≥37.5℃ in the present study, compared with ≥37.2℃ in the retrospective study. Since healthcare providers are not always at the homes of patients unlike in nursing homes and the temperatures of patients cannot be measured every day, some fevers might not have been reported to medical staff. In addition to regular temperature measurements by visiting nurses and/or trained home helpers, family members measured temperatures when they felt that the patient seemed ill. We considered that many such unreported events did not require medical services. That is, the events determined herein had been recognized by medical staff as being evident problems. Although fever might have been under-reported, we considered that the events analyzed herein were thought to be true to the home-medical care setting. Another potential limitation is the lack of vaccination data. Japanese elderly people are arbitrarily vaccinated against such as pneumonia and influenza. These vaccines might be a confounder of fever and/or outcome.

Implications for future research

The need for home medical care will probably increase as the number of aged persons increases in many countries. Because healthcare providers are not always available on demand for those under home medical care, events such as fever might increase concerns about health for patients and their families, and the burdens on healthcare

providers might increase similarly to those in nursing homes [22]. Doctors regularly attend patients at home according to the Japanese system of home medical care, whereas nurses assume this role in some other countries [23-25]. Many such nurses have undergone specialized training [24-26] and their ability to manage patients at home might be equivalent to that of doctors in Japan. However, extrapolation to other countries, or even other areas in Japan, might be difficult due to variations in social/medical circumstances. Therefore, further studies should investigate the issues addressed herein in other settings.

Conclusion

The incidence of fever among home-dwelling elderly patients was 2.5/1000 patient-days, with fever occurring in about one-thrid of the participants within a period of one year. Fever is more likely to occur among individuals with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. Thus health care providers should consider these conditions and should measure the temperatures of elderly residents with lower objective functional status more frequently. The top three causes of fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. The rate of pneumonia/bronchitis was particularly high. Strategies to prevent pneumonia from arising should be targeted at home-dwelling elderly persons with low ADL and/or cognitive function.

Table 1. Diagnosis based on previously defined criteria.

Diagnosis	Criteria
Pneumonia	At least two of the following: ・Fever ・Tachypnea (respiratory rate ≥ 25/min) ・Cough ・Pleuritic chest pain ・Crackles, wheezes or bronchial breath sounds ・Decreased level of consciousness or increased confusion ・Dyspnea ・Tachycardia (pulse rate ≥ 100/min) ・New or worsening hypoxemia ($SpO_2 \leq 91\%$)
Urinary tract infection	At least three of the following without an indwelling catheter: ・Fever or chills ・New or increased burning pain on urination ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine and worsening mental function At least two of the following signs with an indwelling catheter: ・Fever or chills ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine

	• Worsening mental function
Skin and soft tissue infection	At least two of the following: • Fever • Red skin • Hot skin • Painful skin • Skin swelling • Pus discharge

Table 2. Basic attributes of participants.

Participants (n = 419)	Male (n = 166)
Mean age ± SD (years) at start of follow-up	83.4 ± 8.3
Total observation person-days	91,415
Average observation ± SD (days)	217.1 ± 133.0
Median observation (range) (days)	237 (1–365)
Activities of daily living (n)	J1-A2:185 B1-C2:234
Cognition (n)	0-I: 161 IIa-M:258
Level of care-need (n)	
Support-need to care-need level 2	189
Care-need level 3 to 5	224
Gastrostoma (n)	21
Respiratory device (n)	2
Domiciliary oxygen therapy (n)	28
Charlson Comorbidity Index ± SD	2.7 ± 2.0

Table 3. Proportional hazards model for fever.

Model 1

Variable	Hazard ratio (95%CI)	P
Age	1.02 (1.00–1.04)	0.11
Sex (F vs. M)	0.93 (0.65–1.34)	0.71
Activities of daily living (WB or bedridden vs. ambulatory)	1.88 (1.27-2.78)	<0.01
Cognition (moderate-severe vs. none-mild)	1.69 (1.12-2.57)	0.01
Gastrostoma	1.49 (0.81-2.75)	0.20
Respirator	7.77 (2.42-24.97)	<0.01
Domiciliary oxygen therapy	0.74 (0.34-1.63)	0.46
Charlson Comorbidity Index	1.10 (1.01–1.21)	0.03
WB, wheelchair-bound or bedridden vs. ambulatory.		N=419

Model 2

Variable	Hazard ratio (95%CI)	P
Age	1.03 (1.004–1.05)	0.02
Sex (F vs. M)	1.03 (0.70–1.50)	0.88
Care-need level(≥ 3 vs. ≤ 2)	4.49 (2.88-6.99)	<0.01
Gastrostoma	1.32 (0.74-2.34)	0.35
Respirator	6.26 (2.95-13.29)	<0.01
Domiciliary oxygen therapy	0.64 (0.29-1.44)	0.28
Charlson Comorbidity Index	1.11 (1.02–1.21)	0.01
		N=413*

*Care-need levels were not determined in six participants and thus data from 413 patients were analyzed in model 2.

Acknowledgments

This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine, and won the First Prize at the Japan Primary Care Association 2nd Conference. Guidance was received from the Jikei Clinical Research Program for Primary Care at Jikei University School of Medicine. We thank all the staff at Seikyo Ukima Clinic, Kajiwara Clinic, Seikyo Clinic, Kita-adachi Seikyo Clinic and Akabanehigashi Clinic for providing valuable support.

Contributors: KY and MM contributed equally to this study. KY designed the study and participated in study implementation, data collection, data analysis and writing the manuscript. He also serves as guarantor. MM analyzed the data and drafted the manuscript. TW and YF participated in study design, implementation, and data collection. ST participated in study design and writing the manuscript. All authors had

full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. The study hypothesis arouse before inspection of the data

Funding: This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine. The study sponsor had no role in the study design, data collection, analysis and interpretation, writing the report, or the decision to submit the article for publication. All authors are independent of the funding sources.

Competing interests: None

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

Ethical approval: The Ethics Committee at Tokyo Hokuto Health Co-operative (Tokyo, Japan) approved the study (number 32/2009).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

Figure legend

Figure 1

(A) Judgment of degree of independent daily living among disabled elderly persons.

(B) Judgment of degree of independent daily living among elderly persons with dementia.

Figure 2

(A) Cumulative incidence function for the first onset of fever estimated by competing risk method

(B) Comparison of cumulative incidence functions for the first onset of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants

(C) Comparison of cumulative incidence functions for the first onset of fever between participants with moderate-severe (IIa-M) and none-mild (0-I) cognitive impairment.

(D) Comparison of cumulative incidence functions for the first onset of fever between participants with care-need levels ≤2 and ≥3

References

1) Ministry of Health, Labour and Welfare Central Social Insurance Medical Council. Available at: http://www.mhlw.go.jp/stf/shingi/2r9852000001qd1o.html.
2) Ministry of Health, Labour and Welfare. Implementation of home visit. Available at: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/zaitaku/index.html.
3) National Federation of Health Insurance Societies. Investigation research report for medical care service at home. Tokyo; 2008. p. 1-172.
4) Ishibashi R, Hayashi H, Katagiri J, Io K. For death at home. Hospice and Home Care. 2009;17(1):17-21 (in Japanese).
5) Norman DC. Fever in elderly. Clin Infect Dis. 2000;31:148-51.
6) Yokobayashi K, Matsushima M, Fujinuma Y. Retrospective cohort study of the incidence and risk of fever in elderly people living at home: A pragmatic aspect of home medical management in Japan. Geriatr Gerontol Int. 2013;13:887-93.
7) Bentley DW, Bradley S, High K. Practice guideline for evaluation of fever and infection in long-term care facilities. Clin Infect Dis. 2000;31:640-53.
8) Zimmerman S, Gruber-Baldini AL, Magaziner J. Nursing Home Facility Risk Factors for Infection and Hospitalization: Importance of Registered Nurse Turnover, Administration, and Social Factors. J Am Geriatr Soc. 2002;50:1987-95.
9) Smith PW, Bennett G, Bradley S. Infection prevention and control in the long-term care facility. Am J Infect Control. 2008;36:504-35.
10) High K, Bradley S, Gravenstein S. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities. Clin Infect Dis. 2009;48:149-71.
11) Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999;43:S9-18.
12) Guideline for The Diagnosis and Management of Nursing Home Acquired Pneumonia. Alberta Medical Association, 2008.

13) Loeb M, McGeer A, McArthur M. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999; 159(17): 2058-64.

14) Stevens DL, Bisno AL, Chambers HF. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. Clin Infect Dis. 2005;41:1373-406.

15) Kamel HK. Managing Urinary Tract Infections in the Nursing Home: Myths, Mysteries and Realities. Internet Journal of Geriatrics and Gerontology. 2004;1. DOI: 10.5580/205c.

16) Nicolle LE. Urinary tract infection in long-term–care facility residents. Clin Infect Dis. 2000;31:757-761.

17) Charlson ME, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

18) Haesook TK, Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clin Cancer Res , 2007;13(2):559-565

19) Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data. Stat in Med, 1993;12:737-751.

20) Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc, 1999;94: 496-509.

21) Togami J, Nakahara M. Relationship between grade of care required and activities of daily living, dementia in elderly of day rehabilitation care. Yanagawariha Fukuoka Kokusai Kiyo 2009;5:57-60.

22) Leibobitz A, Baumoehl Y, Habot B, et al. Management of adverse clinical events by duty physicians in a nursing home. Aging Clinical and Experimental Research 2004;16(4):314-318.

23) Tatara R. Palliative care by primary care team. The Japanese Academy of Home Care Physicians 2009;10(2):144-151.

24) Katayama F. Learning from Hospice at U.S. The Japanese Academy of Home Care Physicians 2009;10(2):152-157.

25) Riwa F. Home medical and nursing care in the U.S. and England. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p.

264-284.

26) Izawa T. Home medical and nursing care at Sweden. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p. 285-305.

Title

Prospective cohort study of fever incidence and risk in elderly persons living at home

Kenichi Yokobayashi (KY)
Assistant Professor
Department of General Internal Medicine, Hiroshima University of Medical Science, Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Masato Matsushima (MM)
Professor
Division of Clinical Epidemiology, Jikei University School of Medicine
3-25-8 Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan

Takamasa Watanabe(TW)
Director
Kita-adachi Seikyo Clinic, Tokyo Hokuto Health Co-operative
3-1-5 Iriya, Adachi-ku, Tokyo, 121-0836, Japan

Yasuki Fujinuma (YF)
Director
Centre for Family Medicine Development, Japanese Health and Welfare Co-operative Federation
3-22-1 Ukima, Kita-ku, Tokyo 115-0051, Japan

Susumu Tazuma (ST)
Professor
Department of General Internal Medicine, Hiroshima University of Medical Science,

Hiroshima, Japan
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan

Corresponding author: Kenichi Yokobayashi
1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-0037, Japan
E-mail: yokobayashiken@gmail.com
Tel:082-257-5461 Fax: 082-257-1597

Keywords: fever, geriatrics, home care, infection, outcome

Word count: 2909 words

Abstract (295words)

Objective: To determine the incidence of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes from a practical standpoint.

Design: Prospective cohort study.

Setting: Five clinics in downtown Tokyo that process an average of 50-200 outpatients/day.

Participants: Patients (n = 419) aged ≥65 years received home medical management from the five clinics between October 1, 2009 and September 30, 2010.

Main outcome measures: Fever (≥37.5°C or ≥1.5°C above usual body temperature), diagnosis at onset and outcomes (cure at home, hospitalization, death).

Results: The incidence of fever was 2.5/1000 patient-days (95% CI, 2.2 to 2.8). Fever occurred at least once (229 fever events) in 45.5% of the participants during the study period. Fever was more likely to arise in wheelchair-bound or bedridden than ambulatory individuals, with a risk ratio of 1.9 (hazard ratio 1.8 (95% CI 1.3 to 2.6; $P <$ 0.01), in moderate-to-severe than in none-to-mild cognitive impairment (risk ratio, 1.8; hazard ratio [HR], 1.7 (95% CI 1.1 to 2.5, $P = 0.01$) and in those whose care-need levels were ≥3 than ≤2 (risk ratio, 3.4; HR, 4.2 (95% CI 2.8 to 6.3; $P < 0.01$). The causes of fever were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and the common cold (n = 13). Fever was cured in 67% and 23% of patients at home and in hospital, respectively, and 5% of patients each died at home and in hospital. Antimicrobial agents treated 153 (67%) events in the home medical care setting.

Conclusions: Fever was more likely to occur in those requiring higher care levels and

the main cause of fever was pneumonia/bronchitis. Health care providers should consider the conditions of elderly residents with lower objective functional status.

Article summary

Strengths and limitations of this study

- This is the first prospective, multicenter study to describe the status of fever among home-dwelling elderly.
- The present study revealed the incidence and risk factor of fever among elderly persons under home medical management, diagnosis at fever onset and outcomes.
- Some fever occurrences might have remained undetected.

Introduction

In the face of a rapidly aging population combined with a diminishing number of children, the numbers of facilities to care for the elderly and of hospitals that can accept inpatients in Japan are inadequate[1]. The predicted death toll for 2030 is 1.6 million, but where 400,000 of these deaths will occur has not been predicted[1]. Under these conditions, the Ministry of Health, Labour and Welfare in Japan has promoted home medical care/management rather than in-hospital care[2].

In the Japanese home medical care system, physicians regularly make house calls to patients. Doctors regularly visit patients at home for about 20 min twice each month. Patients or their relatives can call for an emergency home visit on demand according to medical emergencies[3]. The leading objectives of medical care at home are to manage brain and nervous system disorders, such as the sequelae of cerebral infarction, Parkinson's disease and dementia, followed by those with cardiovascular disorders, respiratory disorders and malignant neoplasms[3].

Among the elderly receiving home medical care, the major issues comprise fever and infection that impose heavy burdens on not only patients and their relatives, but also medical professionals, since events related to fever reportedly account for many nighttime home visits in Japan[4]. However, because healthcare providers are not always available to patients at home, unlike those in nursing homes[2], the actual incidence and frequency of infection can be difficult to ascertain. Thus, the incidence, risk factors and causes of fever need to be determined. Although the incidence of fever should be high because immune function decreases with aging and chronic comorbidity[5], only our previous retrospective study has shown a fever incidence of 2.3/1000 patient-days among home-dwelling elderly[6]. The reported incidence of

infection in nursing homes is quite similar to that in the home setting (~4.1/1000 patient-days)[7]. However, the incidence of fever per se in nursing homes has not apparently been defined. In addition, we previously found that fever was more likely to occur in individuals with high care-need levels and the three most common causes were pneumonia/bronchitis, urinary tract, and skin and soft tissue infections[6].These three causes were similar to those identified by studies at nursing homes[8-11].

However, the results of our previous retrospective cohort study at a single institution might not have been generally applicable. In addition, most information was obtained from medical records and thus the possibility cannot be ruled out that fever incidences were under-reported, and that measurements of risk factors and judgments regarding the causes of fever were inaccurate.

Thus, the present multicenter prospective cohort study aimed to determine the incidence of fever among elderly persons under home medical management, diagnosis at the time of fever onset and termination (cure at home, hospitalization, death) from a pragmatic standpoint. Whether or not level of care-need, ADL and cognitive function can predict the onset of fever was also assessed.

Methods

Study design

Prospective cohort study.

Setting

The study was implemented at Seikyo Ukima, Kajiwara, Seikyo, Kita-adachi Seikyo and Akabanehigashi clinics that serve the 23 wards of Tokyo. All are located in residential areas within 15 km of downtown Tokyo (Tokyo Station) and are teaching

clinics for senior residency programs in family doctor training. Two to five full-time doctors at these clinics process an average of 50 to 200 outpatients per day (as of April 2012).

Participants

The participants comprised all patients aged ≥65 years who were medically managed at home by physicians at the above 5 center clinics.

Follow-up

The selected patients were followed up between October 1, 2009 and September 30, 2010. Data from patients who could not be followed up because of hospitalization, moving, entering a facility or death were censored. However, follow up was restarted from the date when individuals who were hospitalized during follow up returned to medical management at home.

End-point

The end-points were onset of fever (≥37.5°C or ≥1.5°C above the individual's normal body temperature), diagnosis at onset and termination of fever (cured at home, hospitalized, death). To precisely determine fever rates, the investigators measured the temperatures of the participants at least once every two weeks and questioned the patients and their families about fever occurrences during the previous two weeks.

Because the three most common causes of fever at nursing homes comprised pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection, patients with fever were diagnosed using criteria based on examples from published studies of nursing homes (Table 1)[8, 12-16]. Physicians diagnosed all other diseases.

Prediction and adjustment variables

Age, sex, level of care needed, activities of daily living (ADL), cognitive function, Charlson Comorbidity Index (CCI), and medical devices (gastric fistula, domiciliary oxygen therapy, respiratory devices) were recorded or measured.

The Japanese Long-Term Care Insurance system classifies the needs of individuals aged ≥65 years as requiring constant care due to being bedridden or having dementia, requiring some support for ADL, such as help with housework or physical help, and those who might deteriorate into a state that requires constant care, and not having either of these criteria[1, 2]. This care-need classification is linked to the amount of care service benefits. Uniform criteria are applied nationwide to make objective determinations. Mental and physical status is initially examined (certification examination) by a municipal certification examiner, and then a computer reaches a decision (primary decision) based on the primary physician's written opinion, which includes medical and nursing care judgments, ADL and cognitive function determined by the individual's regular doctor (Figure 1). A care-need certification committee comprising experienced professionals in public health, medicine and welfare reach a decision (secondary decision) based on the primary decision as well as the written opinion of the primary physician and then individuals are classified as having care-need levels from 1 to 5, support need or neither. The value for level of care-need increases as more care is needed, such as that for bedridden patients or those with dementia. Most individuals at care-need level 5 are usually bedridden.

The influence of confounding by comorbidities was adjusted using the Charlson comorbidity index, which is a scored indicator of comorbid disease that can estimate prognosis after one year[17]. Comorbidities are assigned a predetermined score, such as one for myocardial infarction history and dementia, two for hemiplegia and solid cancer

without metastasis, and six for metastatic solid cancer. Higher total scores are associated with higher mortality one year later.

Statistical analysis

The incidence density of fever is shown using the person-time method, together with 95% confidence intervals (CI). This included multiple-failure events, which means all events of fever were counted over the period of home medical care. The period of hospital admission was excluded from the denominator for calculating incidence density.

In contrast, only the first episode of fever was considered in survival analyses since some participants experienced hospital admissions hampering home medical care and stayed there, which may have an effect on risk of fever after the discharge from hospital. Therefore, we did not employ multiple failure-time data in the survival analyses. Instead we treated hospital admission as well as death as competing risk event of fever in the survival analyses using competing-risk method [18].

The cumulative incidence of first fever occurrence was determined using competing-risk method. Between-group comparisons of cumulative incidence were assessed using the method developed by PePe and Mori[19].

To evaluate an independent effect of care-need level, ADL, cognitive function and medical devices on the occurrence of fever event, competing-risks regression was employed considering death and hospital admission as competing risk [20]. Cognitive function and ADL closely correlated with level of care-need [21] and thus were separately analyzed. Model 1 included sex, age, ADL, cognitive function, CCI and medical devices (gastric fistula, domiciliary oxygen therapy, and respirator). Model 2 included sex, age, care-need level, CCI and medical devices.

The level of significance was established at $P < 0.05$ for all tests.

As the primary objective of this study was a description of incidence, we did not perform the exact sample size calculation. The priority was the participation of multiple clinics to expand the external validity. Based on the result of our previous retrospective cohort study [6], moreover, 95% confidence interval of estimation was expected to be sufficiently narrow when including multiple institutions.

Statistical analyses were carried out using STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) .& 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Ethical responsibilities

The Ethics Committee at Tokyo Hokuto Health Co-operative approved the present protocol.

Results

The proportion of 419 eligible and registered participants who required support or care during the one-year study period was the same as the national average (Table 2). Since all of them were followed up until the day they were hospitalized, moved or entered a residence facility or died, the follow-up rate was 100%.

Overall, the total number of fever occurrences that occurred among 91,415 person-days was 229. Therefore, the incidence of fever was 2.5/1000 patient-days (95% CI, 2.2 to 2.8). Cumulative incidence after 1 year follow-up estimated by competing risk method was 0.37 (95%CI, 0.32 to 0.42). Fever occurred at least once among one-third of the patients over the study period of one year (Figure 2A).

Figure 2B compares the cumulative incidence function for the first onset of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants. Fever was significantly more likely to occur in wheelchair-bound or bedridden, than ambulatory individuals ($p<0.01$). After adjustments for sex, age, cognitive function, CCI and medical devices (gastric fistula, domiciliary oxygen therapy, respirator) using the competing-risks regression, the hazard ratio for wheelchair-bound or bedridden and ambulatory participants was 1.9 (95% CI 1.3 to 2.8, $P < 0.01$; Table 3 model 1).

Also, Figure 2C compares the cumulative incidence function for the first onset of fever between individuals with moderate-severe (IIa-M) and none-mild (0- I) cognitive impairment. Fever was significantly more likely to occur in those with moderate-to-severe, than with none-to-mild cognitive impairment ($p<0.01$). After adjustments for sex, age, ADL, CCI and medical devices using the competing-risks regression, the hazard ratio for moderate-severe and none-mild cognitive impairment was 1.7 (95% CI 1.1 to 2.5, $P = 0.01$; Table 3 model 1).

Figure 2D compares the cumulative incidence function for the first onset of fever between individuals with care-need levels ≤2 and ≥3. Fever was significantly more likely to occur in those with care-need levels ≥3 than ≤2 ($p<0.01$). After adjustment for sex, age, CCI and medical devices using the competing-risks regression, the hazard ratio [HR] for ≥3 and ≤2 was 4.5 (95% CI, 2.9 to 7.0, $P < 0.01$; Table 3 model 2).

The leading causes among all 229 fever events were pneumonia/bronchitis (n = 103), skin and soft tissue infection (n = 26), urinary tract infection (n = 22) and common cold (n = 13). The fever outcomes comprised cure at home (67%) or at hospital (23%) and death at home (5%) or in hospital (5%). Of the 229 events, 153 (67%) were treated in the home medical care setting using antimicrobial agents.

Discussion

This multicenter prospective cohort study revealed an incidence of fever among home-dwelling elderly of 2.5/1000 patient-days, and about one-thrid of the patients experienced a fever during a period of one year. Fever was more likely to occur among patients with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. The conditions most likely to cause fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. These issues have only been investigated until now in a single-institution retrospective cohort study[6].

The retrospective cohort study showed that fever was more likely to occur in patients requiring higher care-need levels. The Japanese Long-Term Care Insurance system classifies elderly persons living at home based on ADL and cognitive function as having care-need levels of 1 to 5, support need or neither[1, 2]. These indicators of need for support and care that are equally assessed in most individuals at the start of home medical care in the Japanese medical system, appear to comprise a distinct risk factor for the subsequent occurrence of fever events, but this was only apparent in Japan. This prospective study showed that ADL and cognitive function are sufficiently adaptable to also be considered as significant risk factors for fever events outside Japan. Fever was significantly more likely to occur in wheelchair-bound or bedridden and moderate-severe cognitive impairment, which means health care providers should consider these conditions and should measure the temperatures of elderly residents with lower objective functional status more frequently. Since elderly patients with lower

ADL or cognitive function were more likely to develop pneumonia, its prevention via improving oral care or by pneumococcal vaccination should be useful for such patients.

Strengths and limitations of the study

The main strength of the present study is that it is the first prospective, multicenter effort to determine the status of fever among home-dwelling elderly. Several studies outside Japan have investigated these issues in nursing homes, which are considered fairly similar to home settings. However, we previously discovered the likely incidence and risk of fever in elderly people living at home in a retrospective cohort study at a single Japanese institution [6]. The present multicenter study corrected the sample deviation associated with single facility studies. The prospective study design must have reduced underreported fever events compared with the retrospective study and ADL and cognitive functions could be determined, unlike in the retrospective study.

Our retrospective study uncovered the leading causes of fever among elderly patients under home medical care. The top three sources were pneumonia/bronchitis, urinary tract infection, and skin and soft tissue infection, as they are in nursing homes outside Japan. However, that was a retrospective cohort study at a single institution and these diagnoses was obtained from medical records, and thus judgments regarding the causes of fever might be inaccurate. The present prospective study is reliable because these three source diseases were determined based on predefined criteria using examples from published studies of nursing homes [8, 12-16] (Table 1).

Our study has some limitations. Even if the prospective study increased the frequency of fever, some occurrences might have remained undetected. Information about fever in

the previous retrospective cohort study was obtained from medical records and thus fever was probably underestimated. We improved the detection rate by taking the temperatures of the patients at least once every two weeks and questioning the patients and their families about fever during the previous two-week interval. However, the incidence of fever increased only from 2.3 to 2.5. A possible reason for this is that fevers were defined as temperatures ≥37.5℃ in the present study, compared with ≥37.2℃ in the retrospective study. Since healthcare providers are not always at the homes of patients unlike in nursing homes and the temperatures of patients cannot be measured every day, some fevers might not have been reported to medical staff. In addition to regular temperature measurements by visiting nurses and/or trained home helpers, family members measured temperatures when they felt that the patient seemed ill. We considered that many such unreported events did not require medical services. That is, the events determined herein had been recognized by medical staff as being evident problems. Although fever might have been under-reported, we considered that the events analyzed herein were thought to be true to the home-medical care setting. Another potential limitation is the lack of vaccination data. Japanese elderly people are arbitrarily vaccinated against such as pneumonia and influenza. These vaccines might be a confounder of fever and/or outcome.

Implications for future research

The need for home medical care will probably increase as the number of aged persons increases in many countries. Because healthcare providers are not always available on demand for those under home medical care, events such as fever might increase concerns about health for patients and their families, and the burdens on healthcare

providers might increase similarly to those in nursing homes [22]. Doctors regularly attend patients at home according to the Japanese system of home medical care, whereas nurses assume this role in some other countries [23-25]. Many such nurses have undergone specialized training [24-26] and their ability to manage patients at home might be equivalent to that of doctors in Japan. However, extrapolation to other countries, or even other areas in Japan, might be difficult due to variations in social/medical circumstances. Therefore, further studies should investigate the issues addressed herein in other settings.

Conclusion

The incidence of fever among home-dwelling elderly patients was 2.5/1000 patient-days, with fever occurring in about one-thrid of the participants within a period of one year. Fever is more likely to occur among individuals with care-need levels ≥3 than ≤2, those who are wheelchair-bound or bedridden than ambulatory, and those with moderate to-severe than none-mild cognitive impairment. Thus health care providers should consider these conditions and should measure the temperatures of elderly residents with lower objective functional status more frequently. The top three causes of fever were pneumonia/bronchitis, skin and soft tissue infection, and urinary tract infection. The rate of pneumonia/bronchitis was particularly high. Strategies to prevent pneumonia from arising should be targeted at home-dwelling elderly persons with low ADL and/or cognitive function.

Table 1. Diagnosis based on previously defined criteria.

Diagnosis	Criteria
Pneumonia	At least two of the following: ・Fever ・Tachypnea (respiratory rate ≥ 25/min) ・Cough ・Pleuritic chest pain ・Crackles, wheezes or bronchial breath sounds ・Decreased level of consciousness or increased confusion ・Dyspnea ・Tachycardia (pulse rate ≥ 100/min) ・New or worsening hypoxemia ($SpO_2 \leq 91\%$)
Urinary tract infection	At least three of the following without an indwelling catheter: ・Fever or chills ・New or increased burning pain on urination ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine and worsening mental function At least two of the following signs with an indwelling catheter: ・Fever or chills ・New flank or suprapubic pain or tenderness ・Changes in characteristics of urine

	• Worsening mental function
Skin and soft tissue infection	At least two of the following: • Fever • Red skin • Hot skin • Painful skin • Skin swelling • Pus discharge

Table 2. Basic attributes of participants.

Participants (n = 419)	Male (n = 166)
Mean age ± SD (years) at start of follow-up	83.4 ± 8.3
Total observation person-days	91,415
Average observation ± SD (days)	217.1 ± 133.0
Median observation (range) (days)	237 (1–365)
Activities of daily living (n)	J1-A2:185 B1-C2:234
Cognition (n)	0-I: 161 IIa-M:258
Level of care-need (n)	
Support-need to care-need level 2	189
Care-need level 3 to 5	224
Gastrostoma (n)	21
Respiratory device (n)	2
Domiciliary oxygen therapy (n)	28
Charlson Comorbidity Index ± SD	2.7 ± 2.0

Table 3. Proportional hazards model for fever.

Model 1

Variable	Hazard ratio (95%CI)	P
Age	1.02 (1.00–1.04)	0.11
Sex (F vs. M)	0.93 (0.65–1.34)	0.71
Activities of daily living (WB or bedridden vs. ambulatory)	1.88 (1.27-2.78)	<0.01
Cognition (moderate-severe vs. none-mild)	1.69 (1.12-2.57)	0.01
Gastrostoma	1.49 (0.81-2.75)	0.20
Respirator	7.77 (2.42-24.97)	<0.01
Domiciliary oxygen therapy	0.74 (0.34-1.63)	0.46
Charlson Comorbidity Index	1.10 (1.01–1.21)	0.03
WB, wheelchair-bound or bedridden vs. ambulatory.		N=419

Model 2

Variable	Hazard ratio (95%CI)	P
Age	1.03 (1.004–1.05)	0.02
Sex (F vs. M)	1.03 (0.70–1.50)	0.88
Care-need level(≥ 3 vs. ≤ 2)	4.49 (2.88-6.99)	<0.01
Gastrostoma	1.32 (0.74-2.34)	0.35
Respirator	6.26 (2.95-13.29)	<0.01
Domiciliary oxygen therapy	0.64 (0.29-1.44)	0.28
Charlson Comorbidity Index	1.11 (1.02–1.21)	0.01
		N=413*

*Care-need levels were not determined in six participants and thus data from 413 patients were analyzed in model 2.

Acknowledgments

This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine, and won the First Prize at the Japan Primary Care Association 2nd Conference. Guidance was received from the Jikei Clinical Research Program for Primary Care at Jikei University School of Medicine. We thank all the staff at Seikyo Ukima Clinic, Kajiwara Clinic, Seikyo Clinic, Kita-adachi Seikyo Clinic and Akabanehigashi Clinic for providing valuable support.

Contributors: KY and MM contributed equally to this study. KY designed the study and participated in study implementation, data collection, data analysis and writing the manuscript. He also serves as guarantor. MM analyzed the data and drafted the manuscript. TW and YF participated in study design, implementation, and data collection. ST participated in study design and writing the manuscript. All authors had

full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. The study hypothesis arouse before inspection of the data

Funding: This study was supported by a 2008 research grant from the Japanese Academy of Family Medicine. The study sponsor had no role in the study design, data collection, analysis and interpretation, writing the report, or the decision to submit the article for publication. All authors are independent of the funding sources.

Competing interests: None

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

Ethical approval: The Ethics Committee at Tokyo Hokuto Health Co-operative (Tokyo, Japan) approved the study (number 32/2009). Informed consent for the patients was obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

Figure legend

Figure 1

(A) Judgment of degree of independent daily living among disabled elderly persons.

(B) Judgment of degree of independent daily living among elderly persons with dementia.

Figure 2

(A) Cumulative incidence function for the first onset of fever estimated by competing risk method

(B) Comparison of cumulative incidence functions for the first onset of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants

(C) Comparison of cumulative incidence functions for the first onset of fever between participants with moderate-severe (IIa-M) and none-mild (0-I) cognitive impairment.

(D) Comparison of cumulative incidence functions for the first onset of fever between participants with care-need levels ≤2 and ≥3

References

1) Ministry of Health, Labour and Welfare Central Social Insurance Medical Council. Available at: http://www.mhlw.go.jp/stf/shingi/2r9852000001qd1o.html.
2) Ministry of Health, Labour and Welfare. Implementation of home visit. Available at: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/zaitaku/index.html.
3) National Federation of Health Insurance Societies. Investigation research report for medical care service at home. Tokyo; 2008. p. 1-172.
4) Ishibashi R, Hayashi H, Katagiri J, Io K. For death at home. Hospice and Home Care. 2009;17(1):17-21 (in Japanese).
5) Norman DC. Fever in elderly. Clin Infect Dis. 2000;31:148-51.
6) Yokobayashi K, Matsushima M, Fujinuma Y. Retrospective cohort study of the incidence and risk of fever in elderly people living at home: A pragmatic aspect of home medical management in Japan. Geriatr Gerontol Int. 2013;13:887-93.
7) Bentley DW, Bradley S, High K. Practice guideline for evaluation of fever and infection in long-term care facilities. Clin Infect Dis. 2000;31:640-53.
8) Zimmerman S, Gruber-Baldini AL, Magaziner J. Nursing Home Facility Risk Factors for Infection and Hospitalization: Importance of Registered Nurse Turnover, Administration, and Social Factors. J Am Geriatr Soc. 2002;50:1987-95.
9) Smith PW, Bennett G, Bradley S. Infection prevention and control in the long-term care facility. Am J Infect Control. 2008;36:504-35.
10) High K, Bradley S, Gravenstein S. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities. Clin Infect Dis. 2009;48:149-71.
11) Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999;43:S9-18.
12) Guideline for The Diagnosis and Management of Nursing Home Acquired Pneumonia. Alberta Medical Association, 2008.

13) Loeb M, McGeer A, McArthur M. Risk factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch Intern Med* 1999; 159(17): 2058-64.

14) Stevens DL, Bisno AL, Chambers HF. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. Clin Infect Dis. 2005;41:1373-406.

15) Kamel HK. Managing Urinary Tract Infections in the Nursing Home: Myths, Mysteries and Realities. Internet Journal of Geriatrics and Gerontology. 2004;1. DOI: 10.5580/205c.

16) Nicolle LE. Urinary tract infection in long-term–care facility residents. Clin Infect Dis. 2000;31:757-761.

17) Charlson ME, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

18) Haesook TK, Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clin Cancer Res , 2007;13(2):559-565

19) Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data. Stat in Med, 1993;12:737-751.

20) Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc, 1999;94: 496-509.

21) Togami J, Nakahara M. Relationship between grade of care required and activities of daily living, dementia in elderly of day rehabilitation care. Yanagawariha Fukuoka Kokusai Kiyo 2009;5:57-60.

22) Leibobitz A, Baumoehl Y, Habot B, et al. Management of adverse clinical events by duty physicians in a nursing home. Aging Clinical and Experimental Research 2004;16(4):314-318.

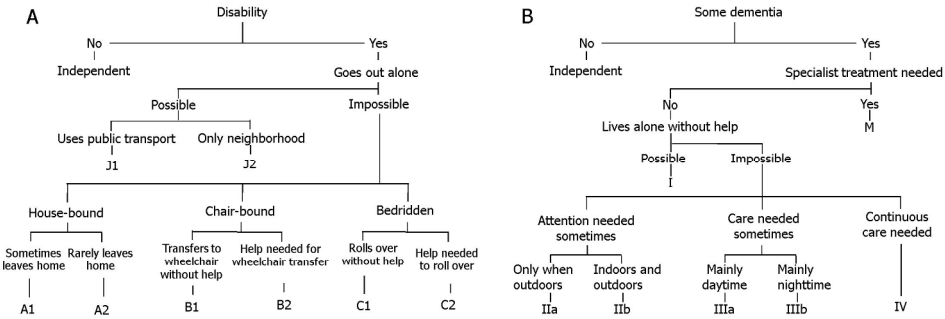
23) Tatara R. Palliative care by primary care team. The Japanese Academy of Home Care Physicians 2009;10(2):144-151.

24) Katayama F. Learning from Hospice at U.S. The Japanese Academy of Home Care Physicians 2009;10(2):152-157.

25) Riwa F. Home medical and nursing care in the U.S. and England. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p.

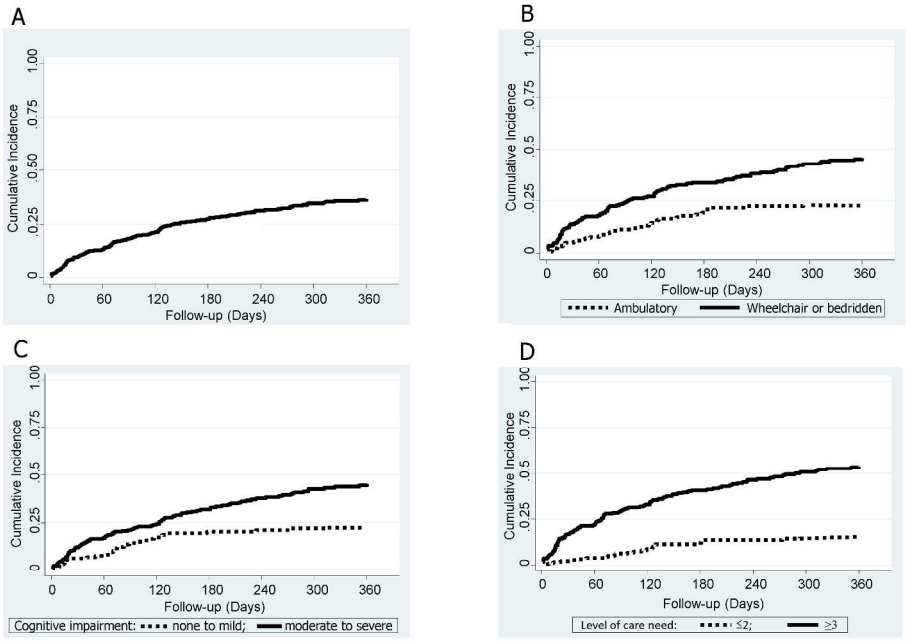
264-284.

26) Izawa T. Home medical and nursing care at Sweden. In: Sato H, Shimazaki K, editors. Tomorrow's Home Care 5. Tokyo: Taiyosha; 2008. p. 285-305.



(A) Judgment of degree of independent daily living among disabled elderly persons.
(B) Judgment of degree of independent daily living among elderly persons with dementia.

199x80mm (300 x 300 DPI)



(A) Cumulative incidence function for the first onset of fever estimated by competing risk method
(B) Comparison of cumulative incidence functions for the first onset of fever between wheelchair-bound or bedridden (B1-C2) and ambulatory (J1-A2) participants
(C) Comparison of cumulative incidence functions for the first onset of fever between participants with moderate-severe (IIa-M) and none-mild (0-I) cognitive impairment.
(D) Comparison of cumulative incidence functions for the first onset of fever between participants with care-need levels ≤2 and ≥3

297x209mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	8, 10-11
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	No sensitivity anayeses

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, 11
		(b) Give reasons for non-participation at each stage	8, 11
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19(Table 2)
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	19(Table 2)
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.