The long-term process change of anxiety / depression in general practice outpatients and examination of their factors
（総合診療外来における不安・抑うつの長期経過後変化とその要因に関する検討）

千葉大学大学院医学薬学府
先端医学薬学専攻
（主任：生坂政臣教授）
島田　史生

Abstract

[Background and objective]

Often patients who come for a consultation at a general practice as outpatients suffer from background anxiety and depression. The psychological state of such patients can alleviate naturally, however, there are cases when these symptoms persist. This study investigated the realities and factors behind anxiety/depression becoming prolonged.

[Methods]

Participants were 678 adult patients, who came to the Department of General Medicine at Chiba University Hospital within a one-year period starting from April 2012 and who completed the Hospital Anxiety and Depression Scale (HADS) during their initial consultation. Participants whose A or D scores in the HADS, or both, were 8 points or higher were defined as being within the anxiety/depression group, with all other participants making up the control group. A telephone interview was also conducted with participants.

Furthermore, age, gender, the period from the onset of their symptoms to the initial Department consultation, the period from the initial Department consultation to the telephone survey, and the existence of mental illness at the final Department diagnosis were investigated.

[Results]

A total of 121 patients (17.8%) agreed to the phone survey. The HADS score during the phone survey showed that the anxiety/depression group had a significantly higher score than the control group. The HADS scores obtained between the initial consultation and telephone survey showed a positive correlation. As factors prolonging anxiety/depression, the logistic regression analysis extracted “Age” and the “continuation of the symptoms during the initial consultation.”

[Conclusion]

The anxiety and depression of general practice outpatients has the possibility of becoming prolonged for an extended period of time; those 65 years or over and those with a continuation of symptoms from the initial consultation are the strongest factors.

Keywords: anxiety, depression, outpatients, general practice.

[Background and objective]

Anxiety and depression are symptoms that are frequently encountered among primary care and general practice outpatients. The frequencies of major depressive disorders and anxiety disorders in a primary care clinic within Japanese urban areas are 3.7% and 4.6%, respectively.[1] This report shows the frequencies of clear-cut depression and anxiety disorders meeting diagnostic standards and that there is a possibility that there are even more so-called "mild cases" that do not meet the diagnostic standards. In reality, patients who suffer from anxiety or depression have physical symptoms, rather than mental symptoms, that appear on the forefront. As such, it is not rare for such patients to consult an outpatient clinic at a department for physical medicine rather than a psychiatric department. According to research by Lépine et al,[2] 57% of patients who exhibited depression consulted a medical institution. Of these, 51% consulted a primary care physician and 12% an expert at a department of physical medicine.[2] Even in Japan, 3.7% of first-time patients at a primary care clinic - that is not indicated to be a psychiatric clinic - suffer from a major depressive disorder, and the main reason for their visit is actually physical symptoms.[1] Depression and anxiety deteriorate quality of life and can amplify patients' physical complaints,[3] as well as increase medical fees.[4] As such, it is very important to detect the existence of anxiety and depression among patients who consult the outpatient department of a primary care or general practice when claiming to suffer from physical complaints.

On the other hand, anxiety/depression patients who do not meet the diagnostic criteria have the possibility of recovering naturally, compared to patients that satisfy the diagnostic standard for major depressive disorders and generalized anxiety disorders. Concerning depression, a study that looked into the general community showed that no symptom was seen, in their follow-up study three years later. Asymptomatic patients at follow-up were 57.4% with major depressive disorders, and 76% for patients with latent depression who possessed psychological symptoms at a level that did not satisfy the diagnostic standards for major depressive disorders.[5] Concerning anxiety, in a follow-up research study of patients who sought consultation as a primary care outpatient, for generalized anxiety disorders – the most severe and common type of anxiety disorder – 43% of the patients showed no symptoms five years later. In contrast, it was 58% of those with anxiety disorders that did not satisfy the diagnostic standard for a particular illness.[6] However, in our experience, it is not rare to encounter depression and anxiety that is prolonged for an extended period of time. On the topic of the factors affecting why anxiety and depression become prolonged for an extended period of time, there have been previous studies by Pietrzak[5] and Jackson et al,[6] who looked at the relationship between the level of anxiety and depression. However, we were not able to find research studies that looked into other factors. In this research, the realities and factors in which anxiety and depression become prolonged among first-time patients of general practice outpatient care were researched and examined.

[Methods]

1. Research participants (Figure 1)

Of the total 979 first-time patients that received consultation at the Chiba University Hospital Department of General Medicine (hereinafter, "the Department") between April 2012 and March 2013, 680 subjects (69.5%) were extracted after excluding 296 patients who did not complete the Hospital Anxiety and Depression Scale (HADS)[7] and 3 patients who had the medicolegal troubles in their medical record. Furthermore, there were 2 patients who had come to see the Department two or

more times within the corresponding period, with all these consultations being their second consultation. With these patients, only the first consultation was counted. As such, 678 participants (69.3%) became the official study participants.

2. Research setting

The Chiba University Hospital is a flagship hospital that is located in central Chiba city, which is located approximately 40 km away from the nation's capital, Tokyo, and has a population of approximately 1 million. This Department conducts consultation of cases that cannot be diagnosed in other hospitals. At the time of the research, the referral rate was approximately 90%, with the diagnosis concordance rate between the Department's diagnosis and the specialist department within the hospital being 82% (Graduate School of Medicine and School of Medicine, Chiba University, Medical School, Medical Department-Affiliated Hospital Achievement List, 2012. Graduate School of Medicine and School of Medicine, Chiba University, Medical Department-Affiliated Hospital, 2014, pp. 151–154). In the Department, a HADS score is given to all first-time patients as a screening process for anxiety and depression.

3. Research Design

This study was designed as a historical cohort study. A telephone survey was conducted with subjects where at least three years had passed from their initial consultation. The telephone survey was conducted by one of the principal authors, the research representative, in order to minimize the difference in the interpretation of the patient's responses if there were different questioners. Furthermore, the participants' intentions for participating in the research study were confirmed at the start of the telephone survey after verbally explaining this study.

The items displayed in Table 1 were investigated with regard to the participants. The survey items were items that were believed to impact the prolonging of anxiety and depression, as determined by a literature search and focus group discussion. Patients that had an A score, D score, or both scores during the initial consultation's HADS testing that was 8 points or higher were defined as belonging to the anxiety/depression group, while all other patients were defined as the control group. Furthermore, among the participants from the anxiety/depression group that still had a high HADS score during the telephone survey (hereinafter, "telephone survey HADS"), in other words, those who had a score of 8 or higher for the A score, D score, or both, were defined as belonging to the "anxiety/depression prolonged group", with all the other subjects belonging to the "depression/anxiety non-prolonged group". A multiple logistic regression analysis was conducted by using the anxiety/depression prolonged group and depression/anxiety non-prolonged group as the dependent variables and the medical record and the telephone survey items (excluding the telephone survey HADS) were the independent variables in order to examine the factors behind the prolongation of the anxiety/depression.

Table 1. Survey item at each stage

During initial consultation	Medical record	During telephone interview
HADS	Age	HADS
	Gender	Presence of new symptoms/diseases after having consulted with the Department
	Number of days from the initial consultation to the telephone survey (range)	Continued presence of symptoms which the subject complained about during the initial consultation
	The period from the onset of symptoms present at the initial consultation to the initial consultation (%)	Has the participant been "doctor shopping" after our examination?
	ICPC Code P status during the final diagnosis at the Department	

4. Survey during the first consultation

HADS can simultaneously evaluate anxiety and depression and comprises of question items that are unlikely to be impacted by physical symptoms. A Japanese edition has been developed and its reliability and validity are being validated.[8,9] Concerning the HADS cut-off value, Bjelland et al[10] reported that if a score of 8 points was used as a cut-off point, sensitivity and specificity were reported to be approximately 80%, respectively.[10] Referencing Bjelland et al's[10] report, this study defined subjects that had either an A score, D score, or both scores, to be 8 points or higher as an anxiety/depression group, with all other participants as the control group.

5. Research of the medical records

Age, gender, the period between the initial consultation at the Department and the telephone survey, the period from the onset of illness to the initial consultation at the Department, and the existence of mental illness during the final diagnosis at the Department were investigated. The existence of mental illness during the final diagnosis at the Department was extracted from the medical record which contained the diagnosis, as determined by a team comprising of one physician who was in charge of the initial consultation with 3 to 5 years of clinical experience, and 1 to 2 medical advisors with 6 or more years of clinical experience. It was then coded using the Primary Care International Categorization Version 2.[11] Owing to the properties of this coding, if a patient suffers from multiple illnesses, multiple ICPC-2 codes will be given to a single patient. In this study, therefore, patients that included psychological/psychiatric illness (Code P) during the final diagnosis were viewed as a "patient with mental illness during the final diagnosis at the Department." The diagnosis of mental illness was conducted based on the Diagnostic and Statistical Manual of Mental Disorders-IV Text Edition.[12]

6. Telephone survey

The subjects were contacted using the phone numbers listed on their medical records. The HADS scoring during the telephone survey used a similar cut-off as the initial consultation HADS, with participants who had 8 points or higher for an A score, D score, or both scores were defined as belonging to the "anxiety/depression prolonged group" with all other patients defined as "anxiety/depression non-prolonged group."

The behavior of browsing and selecting doctors (so-called "doctor shopping") as described in previous Japanese studies[13] is stipulated to include consulting three or more medical institutions regarding the same symptom. In this study, if a patient consulted two or more medical institutions over the same symptom, present during their initial consultation, without referral from the Department,

or in other words, if the patient consulted three or more institutions including the Department – it was defined as doctor shopping behavior. Since the vague recollection can be eliminated as much as possible by limiting the time period, and doctor shopping behavior within the preceding one-year period may have continued even at the time of the research, doctor shopping behavior within one year from the research period was investigated. The emergence of new symptoms/illness was defined as a symptom/function disorder that newly emerged after the initial consultation and continued even at the time of the research. Concerning the existence of symptoms that the participants complained of during their initial consultation, the participants were asked if these complaints persisted during the telephone survey.

7. Statistical analysis

The comparison between the anxiety/depression group and the control group on the baseline characteristics and the survey items were evaluated using Fisher's exact test and the Mann-Whitney U-test. In order to examine the change between the initial HADS and telephone survey HADS for the same subject, a Spearman's correlation coefficient was calculated for the correlation between the initial and telephone survey HADS scores.

The comparison between the anxiety/depression prolonged group and the anxiety/depression non-prolonged group were conducted using Fisher's exact test. For the independent variance of the multiple layer logistic regression analysis, variables that became $P<0.15$ for the single variable analysis in the two groups of the anxiety/depression prolonged group and anxiety/depression non-prolonged group were injected. Furthermore, before the analysis, an examination was conducted using a variance inflation factor (VIF) in order to confirm the issue of multicollinearity.

All statistical analysis was conducted using Easy R (EZR) with the significance interval of each analysis set under 5%. EZR is a freeware program developed by using R, statistical analysis software, as its foundation. As such, its fundamental properties correspond to R.[14] R is used widely for academic research purposes and has a high reliability.[15]

In addition, those who 1) did not add a contact telephone number on the medical record; 2) declined to respond; 3) had passed away, 4) were admitted to another hospital, or 5) could not respond owing to problems with physical/mental faculties, were excluded from the analysis.

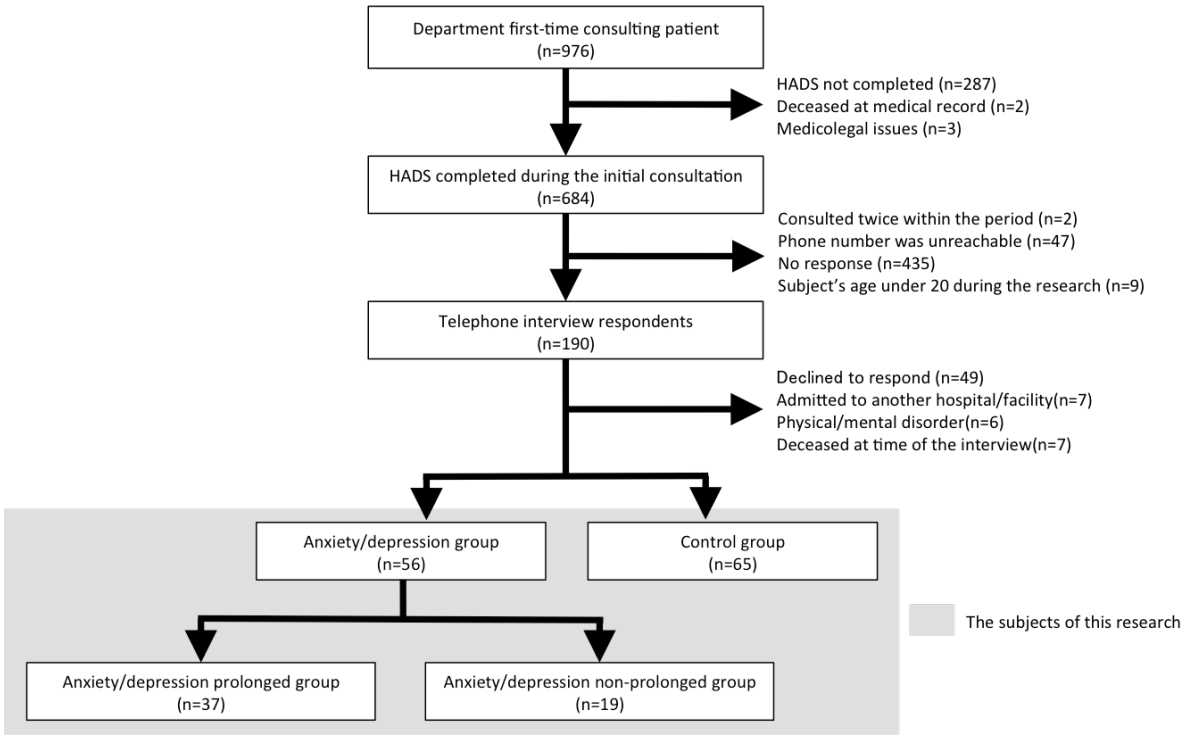
[Results]

1. Respondents outline (Figure 1)

Of the 678 subjects, 192 subjects (28.3%) responded to the phone calls, excluding the 47 subjects who did not use the telephone number provided and 493 subjects who did not respond because of reasons such as not being present. Of the 192 subjects that responded, 48 subjects declined to respond, 9 had passed away at the time of the research, 7 had been admitted to another hospital/facility, and 6 could not respond owing to physical and mental function disorders, and these were all excluded. As a result, valid responses were obtained from 121 subjects (17.8%, 54 males, 67 females, mean age: 69.0 years old).

Fifty-six out of the 121 subjects belonged to the anxiety/ depression group (46.3%, mean age: 67.5 years old), with the control group having 65 subjects (53.7%, mean age: 70.0 years old). Of the 56 subjects in the anxiety/depression group, 37 were in the anxiety/depression prolonging group (66.1%) and 19 in the anxiety/depression non-prolonging group (33.9%).

Figure 1: Outline of the respondents



2. The result of the patient background factor (Table 2) and each research item (Table 3)

No significant difference between the two groups was found for the patient background factor.

The anxiety/depression group had a significantly higher percentage of people who included mental illness in their final diagnosis – in other words, the percentage of the anxiety/depression prolonging group – compared to the control group (P=0.012, P<0.001). No significant difference between the two groups was found in other items.

Table 2. Baseline Characteristics of Each Group. (n=121)

Factor		Anxiety / Depression (n=56)	Control (n=65)	p-value
Age [Range]		67.5 (30 ~ 87)	70.0 (21 ~ 86)	0.307
Age (%)	≥ 65 years	33 (58.9)	46 (70.8)	0.186
Sex (%)	Female	35 (62.5)	32 (49.2)	0.199
Number of days from the initial consultation to the telephone survey (range)		1094.5 (1007 ~ 1295)	1093.0 (981 ~ 1332)	0.956
The period from the onset of symptoms present at the initial consultation to the initial consultation (%)	Chronic	50 (89.3)	51 (79.7)	0.211

Table 3. Results of Evaluation Items (n = 121)

Factor		Anxiety / Depression (n=56)	Control (n=65)	p-value
Doctor Shopping-Behavior (%)	Yes	9 (16.1)	4 (6.2)	0.139
Final diagnosis of our department (%)	Code P (+)	25 (44.6)	15 (22.7)	0.012 *
New symptoms or disease (%)	Emergence	26 (46.4)	29 (44.6)	0.857
Symptom at the time of the first medical examination (%)	Persistence	30 (46.4)	38 (58.5)	0.713
HADS score from the telephone survey (%)	High	37 (66.1)	15 (23.1)	<0.001 *

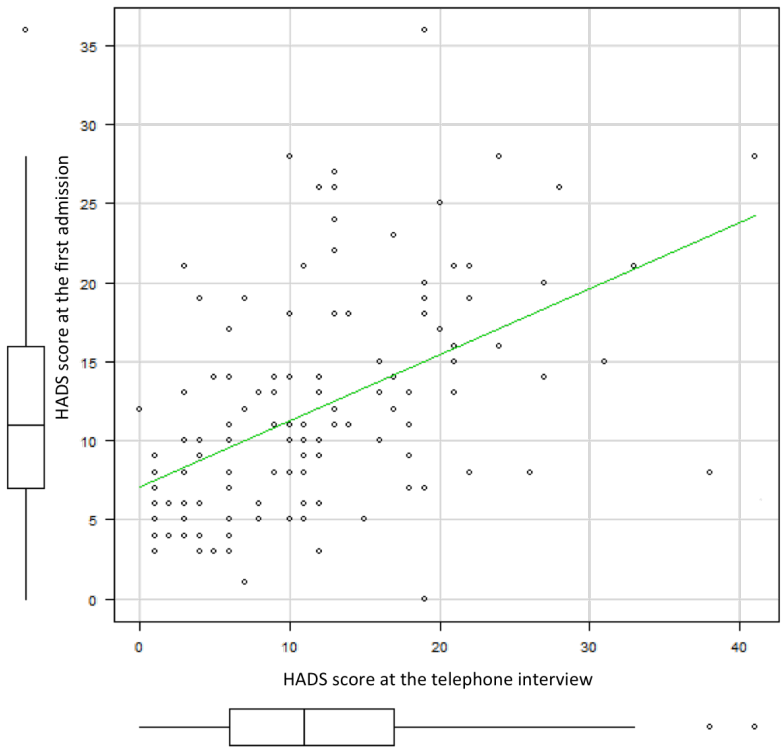
*: p<0.05

3. The relationship between the initial consultation HADS and the telephone survey HADS (Figure 2)

The median of the telephone survey HADS (25 percentile (Q1), 75 percentile (Q3)) for the anxiety/depression group (15 points, Q1: 10.0 points, Q3: 20.3 points) was significantly higher than

that of the control group (7 points, Q1: 4.0 points, Q3, 12.0 points) (P<0.001). A significant correlation was found between the telephone survey HADS and the initial consultation HADS (Figure 2, correlation coefficient: 0.53, P<0.001).

Figure 2. Correlation between initial consultation and telephone survey HADS scores



4. Factors that impact the prolongation of anxiety/depression (Chart 4)

Concerning the survey items on the medical record and phone survey (excluding the telephone survey HADS), a comparative examination between the two groups - anxiety/depression prolonging group and anxiety/depression non- prolonging group - were conducted. Factors that were P<0.15 in a univariate analysis, “Age (65 years and older) (VIF: 1.178),” the presence of “Doctor shopping (VIF: 1.005)”, and “The continuation of the initial symptom (VIF: 1.176)” all had a VIF of under 2 and did not show a variable that displayed a strong line-type relationship. Therefore, the above three items were all injected as independent variables into the multilayered logistic regression analysis. As a result, “Age (65 years old and above)” (Odds ratio (OR): 4.36, 95% confidence interval (CI): 1.16-16.40) and “The remaining of the symptoms during the initial consultation” (OR: 5.72, 95% CI: 1.51-21.70) were extracted as the protraction of anxiety/depression.

Table 4. Impact of Factors on Prolongation of Anxiety / Depression

Univariate Analysis		
	Prolongation rate	p-value
Age		
65< years	52.2%	0.089
≥65 years	75.8%	
Sex		
Female	62.9%	0.572
Male	71.4%	
Duration of disease		
Acute	40.0%	0.324
Chronic	68.6%	
Doctor shopping-behavior		
No	61.7%	0.146
Yes	88.9%	
Final diagnosis		
Code P (-)	61.3%	0.571
Code P (+)	72.0%	
New symptoms		
None	60.0%	0.399
Emergence	73.1%	
Past symptoms		
Disappear	50.0%	0.025
Persistence	80.0%	
Multivariate Analysis		
Age		
≥65 years	4.360 (1.16-16.40)	0.029
<65 years	1	
Past symptoms		
Persistence	5.720 (1.51-21.70)	0.010
Disappear	1	

[Discussion]

This study showed that 66% of the depression/anxiety group displayed anxiety/depression similarly during the telephone survey as they did during the initial consultation. This number is slightly higher compared to that found in preceding research studies.[5,6,16] The study by Forsell[16] examined subjects who were 64 years old or younger, in Pietzak's study[5] 82.5% of participants were 64 years old or younger, and in Jackson et al's[6] study the mean age was 55 years. Compared to these studies, the mean age of the anxiety/depression group of this study was high, at 67.5 years. As will be mentioned later, there is a possibility that anxiety/depression is prolonged among the elderly. The fact that the subjects' mean age was high could be a reason why the percentage of those with prolonged anxiety/depression was high in this study compared to previous studies.

In this study, age (65 years and above) was extracted as a factor behind anxiety/depression prolongation. Subthreshold depression among the elderly is two to three times more common compared to a major depressive disorder, with such depression progressing to a major depressive disorder at a frequency of 8-10% a year.[17] Furthermore, depression that has developed at 65 years or older, compared to depression that has developed at a younger age, has a higher frequency of being accompanied with an anxiety disorder[18] with higher relapse rates,[19] and higher severity levels.[20] These could be attributed as reasons as to why the anxiety and depression of the elderly were prolonged. Therefore, when giving medical consultations to the elderly, treatment that considers properties such as conducting early treatment intervention against anxiety/depression is believed to be important.

Another independent factor that was identified as responsible for prolonged anxiety/depression was the "continuation of the symptoms during the initial consultation." There is no doubt to the argument that an accurate diagnosis for figuring out the appropriate existing treatment method will alleviate the symptoms if the treatments are proven to be effective. However, it is also a fact that even if an appropriate diagnosis has been given, there are illnesses in which the alleviation of its symptom is difficult. For example, for mental illnesses, patients with physically manifesting disorders may believe that their symptoms are caused by an organic disease and have difficulties accepting that they suffer from a mental illness,[21] and are prone to have their condition protracted.[22] Even if the patients suffered from an organic disease, a dramatic improvement of symptoms would be difficult with functional disorders and degenerative diseases. With these illnesses, special consideration such as cognitive behavioral therapy is necessary.

The limitations of this research and future tasks

This study employed a telephone interview method mainly because of the issue of cost. However, the response rate to the telephone interview was low and there is the possibility of there being a bias in the result. Various factors can be attributed to the low response rate. Firstly, the interview time window was limited to 9 AM to 8 PM, which resulted in a poor response rate from employed individuals (in particular, the younger demographic). This is believed to be because this time range coincides with their working hours. Secondly, there were a few cases in which the subject had changed their phone number within the period of a little over three years. As a result of competition between phone carriers in Japan, people often change their phone numbers. This may have been a factor that resulted in many people not responding. The following are possible measures that can be taken in the future:

(1) Heighten the convenience for the respondents by allowing responses to the survey via mail and Internet.
(2) Consider providing incentives to those cooperating in the research, such as sending a compensatory gift, in order to attempt to improve the response rate.

A task for the future includes intervention research on anxiety/depression during the initial consultation. Since the continuation of the symptom after initial consultation was suggested to be a factor of anxiety/depression prolongation, it would be desirable to conduct research on subjects whose symptoms are unlikely to improve, in particular, chronic illness cases.

[Conclusion]

The anxiety/depression of general practice outpatients has the possibility of prolonging for an extended period of time. Elderly patients aged 65 and above, and the symptoms during the initial consultation sustained, have been suggested as factors affecting this symptom prolongation.

[Acknowledgement]

This research study was conducted after obtaining approval from Chiba University Graduate School of Medicine Ethics Committee. Furthermore, the authors do not hold any conflicts of interest that need to be declared.

[References]

1. Yamada K et al. Jpn J Gen Hosp Psychiatry. 2004;16(1):18–23
2. Lépine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research In European Society). *Int Clin Psychopharmacol.* 1997;12(1):19–29.
3. Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. *Psychosom Med.* 1988;50(5):510–519.
4. Katon WJ, Lin E, Russo J, Unutzer J. Increased medical costs of population-based sample of depressed elderly patients. *Arch Gen Psychiatry.* 2003;60(9):897–903.
5. Pietrzak RH, Kinley J, Afifi TO, et al. Subsyndromal depression in the United States: prevalence, course, and risk for incident psychiatric outcomes. *Psychol Med.* 2013;43:1401–1414.
6. Jackson JL, Passamonti M, Kroenke K. Outcome and impact of mental disorders in primary care at 5 years. *Psychosom Med.* 2007;69(3):270–276.
7. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361–370
8. Kitamura T. The Hospital Anxiety and Depression Scale (HADS). Archives of Psychiatric Diagnostics and Clinical Evaluation. 1993;4:371–372.
9. Kugaya A, Akechi T, Okuyama T, Okamura H, Uchitomi. Screening for Psychological Distress in Japanese Cancer Patients. *Jpn J Clin Oncol.* 1998;28(5):333–338.
10. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69–77.
11. World Health Organization. ICPC-2; WONCA International Classification Committee: International Classification of Primary Care Revised Second Edition 2005. Geneva. Accessed 2012.
12. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (Text Revision American Psychiatric Association, Washington, D.C., 2000.
13. Sato T, Takeichi M, Shirahama M, Fukui T, Gude JK. Doctor-shopping patients and users of alternative medicine among Japanese primary care patients. *Gen Hosp Psychiatry.* 1995;17(2):115–125.
14. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452–458.
15. Team RDC. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2011.
16. Forsell Y. A three-year follow-up of major depression, dysthymia, minor depression and subsyndromal depression: results from a populations-based study. *Depress Anxiety.* 2007;24(1):62–65.
17. Meeks TW, Vahia IV, Lavretsky H, Kulkarni G, Jeste DV. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord.* 2011;129(1):126–142.
18. Brown RP, Sweeney Ja, Loutsch E, Frances A. Involutional melancholia revisited. *Am J Psychiatry.* 1984;141(1):24–28.
19. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry.* 2005;162(9):1588–1601.

20. Kessing LV. Differences in diagnostic subtypes among patients with late and early onset of a single depressive episode. *Int J Geriatr Psychiatry.* 2006;21(12):1127–1131.
21. Epstein RM, Quill TE, McWhinnery IR. Somatization reconsidered incorporating the patient's experience of illness. *Arch Intern Med.* 1999;159(3):215–222.
22. Jackson JL, Kroenke K. Prevalence, impact and prognosis of multisomatoform disorder in primary care: a 5-year follow-up study. *Psychosom Med.* 2008;70(4):430–434.

International Journal of General Medicine
平成２８年１２月　投稿中