Community Pharmacists' Measurement of Health-related Quality of Life in Outpatients Taking High-risk Drugs

Takenori Ichimura (✉ ichimura@cmed.showa-u.ac.jp)

Showa University: Showa Daigaku <https://orcid.org/0000-0002-4731-6032>

Chiaki Ogawa

Department of Pharmacy, National Hospital Organization Osaka National Hospital: Kokuritsu Byoin Kiko
Osaka Iryo Center

Hayato Murata

QOL Co., Ltd.

Katsuaki Miyahara

QOL Co., Ltd.

Satoshi Yuge

Nihon Chouzai Co., Ltd.

Ryota Tsukioka

AIN PHARMACIEZ INC.

Keisuke Kado

KRAFT Inc.

Tomonobu Yoshimura

SOGOMEDICAL CO., LTD

Kenichi Suzuki

Division of Applied Pharmaceutical Education and Research, Hoshi University

Hisanaga Nomura

Department of Data Science / Pharmacy, National Cancer Center Hospital East

Hisanori Shimizu

Department of Pharmacy, The Institute Hospital of Japanese Foundation for Cancer Research

Research

Keywords: health-related quality of life, EuroQol-5-dimensions-5-levels, community pharmacist, high-risk drugs

Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-858889/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

1 *Title page*

2 **Community pharmacists' measurement of health-related quality of life in outpatients taking**
3 **high-risk drugs**

4

5 **Author information**

6 Takenori Ichimura,^{1,2} Chiaki Ogawa,^{1,3} Hayato Murata,^{1,4} Katsuaki Miyahara,⁴ Satoshi Yuge,⁵ Ryota
7 Tsukioka,⁶ Keisuke Kado,⁷ Tomonobu Yoshimura,⁸ Kenichi Suzuki,⁹ Hisanaga Nomura,¹⁰ Hisanori
8 Shimizu,^{1,11,12}

9

10 ¹Study group for Comprehensive Cost-Effectiveness Analysis of Pharmacotherapy

11 ²Department of Hospital Pharmaceutics, School of Pharmacy, Showa University

12 ³Department of Pharmacy, National Hospital Organization Tokyo Medical Center

13 ⁴QOL Co., Ltd.

14 ⁵Nihon Chouzai Co., Ltd.

15 ⁶AIN PHARMACIEZ INC.

16 ⁷KRAFT Inc.

17 ⁸SOGO MEDICAL CO., LTD

18 ⁹Division of Applied Pharmaceutical Education and Research, Hoshi University

19 ¹⁰Department of Date Science / Pharmacy, National Cancer Center Hospital East

20 ¹¹Department of Pharmacy, The Institute Hospital of Japanese Foundation for Cancer Research

21 ¹²Department of Nursing, School of Nursing and Rehabilitation Sciences, Showa University

22

23 **Corresponding author**

24 Takenori Ichimura, Department of Hospital Pharmaceutics, School of Pharmacy, Showa University,

25 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

26 E-mail: ichimura@cmed.showa-u.ac.jp

27 Phone number: +91-3-3784-8000

28 FAX number: +91-3-3784-8453

29

30 **Abstract**

31 **Background:** Patients who develop severe side-effects when taking high-risk drugs may have a

32 significantly reduced health-related quality of life (QOL); therefore, it is important to identify

33 changes in health-related QOL in these patients. This study aimed to determine health-related QOL

34 in community pharmacy outpatients taking high-risk drugs.

35 **Methods:** This prospective observational study was conducted at 29 pharmacies in 12 regions and

36 cities in Japan from October to December 2020. Using descriptive questionnaires of EuroQOL-5-

37 dimensions-5-levels (EQ-5D-5L), community pharmacists obtained health-related QOL data from

38 outpatients taking high-risk drugs.

39 **Results:** In total, 760 outpatients were enrolled. The mean health-related QOL of all outpatients was
40 0.869. Health-related QOL decreased with increasing age. Outpatient health-related QOL was 0.700,
41 0.763, 0.785, and 0.817 when taking antiepileptic, antidepressant, digitalis, and antiarrhythmic drugs,
42 respectively, which was lower than the average health-related QOL of all outpatients. Mobility and
43 pain/discomfort accounted for a large proportion of the decline in health-related QOL with
44 increasing age. No difference was found concerning personal care in relation to age; however, the
45 number of outpatients with mobility, normal activity, and pain challenges decreased with age. In
46 contrast, outpatients aged <65 years with anxiety/depression showed lower than overall average
47 health-related QOL.

48 **Conclusion:** Community pharmacists determined the health-related QOL of outpatients taking high-
49 risk drugs. We clarified the contributions of the 5-dimensions.

50 **Trial registration:** UMIN-CTR Study Design: trial Number UMIN 000041942. Registered 30
51 September 2020, <https://www.umin.ac.jp>

52 **Keywords:** health-related quality of life, EuroQol-5-dimensions-5-levels, community pharmacist,
53 high-risk drugs

54

55 **Introduction**

56 Techniques for prolonging life have improved along with advances in medicine, and they
57 have been attributed to the research and development of new drugs and improved healthcare. Recent

58 progress in the development and availability of new drugs has allowed many patients to receive
59 medical treatment in an outpatient setting. Despite the benefits, all drugs have side-effects; however,
60 high-risk drugs require special management by the Ministry of Health, Labor, and Welfare in Japan.
61 High-risk drugs comprise those: (i) that have a narrow therapeutic range, (ii) whose control of the
62 administration method and dosage is challenging owing to the closeness between addiction and
63 effectiveness, (iii) that have high individual differences in pharmacokinetics, (iv) that have high
64 individual differences due to physiological factors (e.g., liver and kidney disorders and physiological
65 differences in older adult patients and in children), and (v) whose improper administration causes
66 serious harm to patients. Furthermore, high-risk drugs comprise those in which medical accidents
67 and incidents have been reported.

68 Many drugs, such as anticancer, anticoagulant, and antidiabetic drugs are established high-
69 risk drugs that require pharmacological management at community pharmacies. When patients
70 taking high-risk drugs develop severe side-effects, their quality of life (QOL) may be significantly
71 reduced; therefore, it is important to identify changes in QOL among those taking high-risk drugs.

72 A health-related QOL scale can be used regardless of the disease or drug. Two methods for
73 scoring health-related QOL have been reported, the profile-type and utility-value scales [1]. There
74 are two methods for measuring the utility value, the direct and indirect measurement methods. The
75 EuroQol instrument was developed by an inter-disciplinary five-country group between 1987 and
76 1991; the EuroQol 5-dimensions-3-levels (EQ-5D-3L) is a tool used for indirect measurement [2].

77 Subsequent to the EQ-5D-3L, the EuroQol-5-dimensions-5-levels (EQ-5D-5L) was developed. The
78 five dimensions comprise mobility, personal care, usual activities, pain/discomfort, and
79 anxiety/depression. The five levels are represented as 1, “no problems”; 2, “slight problems”; 3,
80 “moderate problems”; 4, “severe problems”, and 5, “unable”. Participant responses are converted
81 into a single preference-based score (i.e., a utility value), in which 0 indicates death, and 1 indicates
82 perfect health, based on the Japanese value set. The EQ-5D-3L and EQ-5D-5L are widely used in
83 many countries, especially in Europe. A scoring method for the Japanese version of the EQ-5D-5L
84 has been developed, which enables health-related QOL to be evaluated in Japan based on the EQ-
85 5D-5L [3-5].

86 The Japanese universal health care system covers all Japanese citizens [6]. Health-related
87 QOL is an important factor that can be assessed using the EQ-5D, a relevant approach in the
88 economic evaluation of health technology [7]. Health-related QOL can be measured in phase III
89 clinical trials [8]. Clinical hospital pharmacists in Japan have previously reported the results of
90 measuring inpatient health-related QOL [9, 10]; however, QOL assessment for hospitalized
91 inpatients does not involve a long-term patient QOL assessment. An approach to measure long-term
92 QOL is with the help of community pharmacists. These professionals provide long-term patient drug
93 management, yet there have been few community pharmacy-based reports concerning health-related
94 QOL regarding community pharmacy outpatients taking high-risk drugs. Measurement of patient
95 health-related QOL by community pharmacists may lead to an enhanced understanding of QOL in a

96 real-world setting. This prospective observational study aimed to determine the health-related QOL
97 of community pharmacy outpatients taking high-risk drugs. To the best of knowledge, the QOL of
98 outpatients taking high-risk drugs has not been clarified so far.

99

100 **Methods**

101 *Study design and patients*

102 A prospective observational study was undertaken at 29 pharmacies in 12 regions and cities
103 from October to December 2020 in Japan. Seventy-nine community pharmacists measured
104 outpatients' health-related QOL using the EQ-5D-5L questionnaire. This process was conducted
105 after obtaining informed consent from outpatients who had been prescribed high-risk drugs such as
106 anticancer, immunosuppressive, arrhythmia, antiepileptic, anticoagulant, and digitalis drugs, along
107 with theophylline and potassium; and psychiatric drugs, antidiabetic drugs, pancreatic hormones
108 (insulin), and anti-human immunodeficiency virus drugs. The outpatients were aged ≥ 20 years.
109 Community pharmacists confirmed health-related QOL regardless of whether the prescription was
110 the first, second, or a repeat prescription. Outpatients were enrolled regardless of whether they had
111 previously started treatment.

112

113 *Measurement of health-related QOL using the EQ-5D-5L*

114 Outpatients were asked to respond to the questionnaire during their waiting times. A paper
115 form of the Japanese version of the EQ-5D-5L questionnaire was used [3-5]. The questionnaires
116 were administered by community pharmacists and there was no remuneration for the participants.
117 The community pharmacist who received the EQ-5D-5L questionnaire recorded the responses along
118 with relevant medical data such as age, sex, drugs, drug adherence, and medical history. A EuroQol
119 group (Rotterdam, The Netherlands) license was obtained for research purposes.

120

121 **Results**

122 *Outpatients*

123 The characteristics of the study population are summarized in Table 1. During the survey
124 period, 760 outpatients were enrolled in the study (average age, 68.5 years; men, n = 420 [55.3%];
125 women, n = 340 [44.7%]). The proportion of outpatients aged >65 years, who are considered older
126 adults in Japan, was 68.2%. The proportion of outpatients >75 years, who required more care was
127 35.8%. In total, 760 outpatients were taking an average of four drugs.

128 The most common high-risk drugs were anticoagulant (272 outpatients, 35.8%), anticancer
129 (260 outpatients, 34.2%), and antidiabetic (236 outpatients, 31.1%) drugs.

130

131 *Health-related QOL*

132 The mean health-related QOL value concerning all 760 outpatients was 0.869. The mean
133 health-related QOL value for each outpatient is shown in Table 2.

134 Health-related QOL values were lower in women (0.853) than in men (0.881). The health-
135 related QOL of outpatients aged 40 to 64 years who needed assistance and the health-related QOL of
136 outpatients aged ≥ 65 years were lower than of those among the other age groups.

137 Health-related QOL values according to age were as follows: outpatients aged < 65 years,
138 0.889; outpatients aged 65–69 years, 0.879; outpatients aged 70–74 years, 0.875; outpatients aged
139 75–79 years, 0.862, and outpatients aged > 80 years, 0.829.

140 Older outpatients were found to have a lower health-related QOL, with outpatients aged > 80 years
141 having the lowest health-related QOL.

142 Health-related QOL values according to high-risk drugs were as follows: antidiabetic drugs,
143 0.879; anticoagulant drugs, 0.871; and anticancer drugs, 0.871; all exceeded the average health-
144 related QOL value (0.869) for all outpatients. However, health-related QOL was 0.700 for those
145 taking antiepileptic drugs, 0.763 for those taking antidepressant drugs, 0.785 for those taking
146 digitalis, and 0.817 for those taking antiarrhythmic drugs; these were lower values than the average
147 health-related QOL value for all outpatients. The health-related QOL of 163 patients who did not live
148 alone was 0.850 and 0.787 for 30 patients who lived alone.

149

150 *Values using 5-dimensions-5-levels according to age group*

151 Health-related QOL values according to age group are shown in Figure 1. The EQ-5D-5L
152 consists of five dimensions and five levels. Pain/discomfort had the lowest proportion among all 760
153 outpatients. Mobility and pain/discomfort accounted for a large proportion of the decline in health-
154 related QOL with increasing age. There was no difference in personal care according to age;
155 however, in terms of mobility, normal activity, and pain, the number of outpatients with no problems
156 decreased with age. In contrast, anxiety showed the lowest proportion among those aged <65 years
157 with no health-related QOL difficulties.

158

159 **Discussion**

160 We determined the health-related QOL in community pharmacy outpatients taking high-risk
161 drugs in Japan. This is the first study in Japan to report community pharmacists' investigation of
162 health-related QOL assessment in outpatients taking high-risk drugs. It has been reported that the
163 health-related QOL of the Japanese general population is 0.877 (instrument: EQ-5D-3L) [11]. The
164 health-related QOL in this study was 0.869, which was similar to findings from previous inpatient
165 studies [11], and our findings and those of previous studies are generally in agreement. We consider
166 that advances in supportive care help explain why health-related QOL did not decline in patients
167 with terminal cancer. Furthermore, the possibility of taking oral anticoagulants directly may also
168 explain why the health-related QOL of patients taking antithrombotic drugs did not decrease.
169 However, the health-related QOL of patients taking antiepileptic, antidepressant, and cardiotonic

170 drugs was low, which may have been due to patient anxiety levels. Acceptance of death is one of the
171 stages in patients with cancer, as proposed in Kubler-Ross's five stages of death [12], which may
172 explain these reduced levels of anxiety. For other diseases, it is necessary to conduct research on how
173 patients accept their diagnosis and the subsequent implications for QOL.

174 Health-related QOL relating to the five dimensions of mobility, personal care, usual
175 activities, pain/discomfort, and anxiety/depression was determined for community pharmacy
176 outpatients taking high-risk drugs; this evaluation concerned the effects of each factor on health-
177 related QOL. To our knowledge, no previous studies have reported such findings. When focusing on
178 health-related QOL according to age group, we expected that the mobility dimension would show a
179 decline with age. However, anxiety/depression showed lower than average health-related QOL in
180 those aged <65 years. Young outpatients may be anxious about their illnesses and about how to
181 spend the rest of their lives. This study revealed which of the EQ-5D-5L dimensions contributed to
182 lowering health-related QOL according to age, which may help community pharmacists manage
183 outpatient interventions in future.

184 This study had some limitations. First, the participants were outpatients who had agreed to
185 participate in this prospective observational study; therefore, it is likely that collaborating patients
186 with a good health-related QOL were enrolled, which may have resulted in selection bias.
187 Furthermore, patients who interact more readily with pharmacists may have been selected, which
188 could have further contributed to the selection bias. Second, this study did not consider the duration

189 of high-risk drug administration—some patients might have just started high-risk drug treatments,
190 whereas others might have been taking high-risk drugs for a long time. The duration of treatment
191 may have affected health-related QOL. For patients with cancer, their psychological stage (denial,
192 anger, bargaining, depression, and acceptance) at the time of the questionnaire may have influenced
193 their responses. However, for non-cancer diseases, the duration of drug administration may be a
194 factor affecting a patient's health-related QOL. Although not investigated in this study, the treatment
195 duration may be an important factor.

196 Community pharmacists determined the health-related QOL of outpatients taking high-risk
197 drugs. This exploratory study was the first in which community pharmacists evaluated health-related
198 QOL in outpatients taking high-risk drugs. In the future, a new study will measure health-related
199 QOL four or more times to obtain more accurate values and propose a method that does not reduce
200 health-related QOL. Further, we intend to provide an economic evaluation of health technology
201 using health-related QOL based on the EQ-5D-5L.

202

203 **Conclusion**

204 Using descriptive questionnaires of EuroQOL-5-dimensions-5-levels (EQ-5D-5L),
205 community pharmacists obtained health-related QOL data from outpatients taking high-risk drugs
206 (anticoagulant drugs, anticancer drugs, antidiabetic drugs, arrhythmia drugs, immunosuppressive
207 drugs, psychiatric drugs, pancreatic hormones (Insulin), antiepileptic drugs, theophylline, digitalis,

208 and anti-human immunodeficiency virus drugs). We determined the health-related QOL in
209 community pharmacy outpatients. This is the first study in Japan to report community pharmacists’
210 investigation of health-related QOL assessment in outpatients taking high-risk drugs.

211

212 **Declarations**

213 **Ethics approval and consent to participate:** The study was performed in accordance with the
214 Declaration of Helsinki and was approved by the Ethics Committees of the School of Nursing and
215 Rehabilitation Sciences, Showa University (approval number: 528) and other participating centers.
216 We obtained written informed consent of all patients.

217 **Consent for publication:** Written informed consent was obtained from the patients for anonymized
218 information to be published in this article.

219 **Availability of data and material:** All relevant data are within the manuscript and its supporting
220 information files.

221 **Competing interests:** The authors have no conflicts of interest to declare.

222 **Funding:** The authors received financial support from the Ministry of Health, Labor and Welfare,
223 Health Labor Sciences Research Grant, and Geriatric Oncology Guideline-establishing (GOGGLE)
224 Study Group, which is a public institution in Japan.

225 **Author’s contributions:** Conception and design of study: Takenori Ichimura, Chiaki Ogawa,
226 Hayato Murata, Katsuaki Miyahara, Satoshi Yuge, Ryota Tsukioka, Keisuke Kado, Tomonori

227 Yoshimura, Kenichi Suzuki, and Hisanori Shimizu; analysis and interpretation of the data: Takenori
228 Ichimura and Hisanaga Nomura; drafting of the manuscript: Takenori Ichimura and Hisanaga
229 Nomura; critical revision of the manuscript for important intellectual content: Takenori Ichimura,
230 Chiaki Ogawa, Hayato Murata, Katsuaki Miyahara, Satoshi Yuge, Ryota Tsukioka, Keisuke Kado,
231 Tomonori Yoshimura, Kenichi Suzuki, Hisanaga Nomura, and Hisanori Shimizu; approval of the
232 manuscript to be published: Takenori Ichimura, Chiaki Ogawa, Hayato Murata, Katsuaki Miyahara,
233 Satoshi Yuge, Ryota Tsukioka, Keisuke Kado, Tomonori Yoshimura, Kenichi Suzuki, Hisanaga
234 Nomura, and Hisanori Shimizu.

235 **Acknowledgements:** We would like to acknowledge the investigators among community
236 pharmacists. The investigators are: Ayako Yamaoka, Ryota Kamiya, Yudai Kato, Tomomi Yagi,
237 Toshihiro Hirai, Mika Suga, Naoko Yoshinaga, Sakie Fujihashi, Haruka Matsuo, Sachie Tsuyuki,
238 Satoka Hayashi, Kazuyo Takita, Hiroyuki Fukushima, Minako Kozawa, and Tatsuya Yukioki
239 (QOL Co., Ltd.); Kenichi Takahashi, Chie Tanaka, Chihiro Masumoto, Hiroki Sato, Naoki
240 Shimomura, Yusuke Kawasaki, Fumiko Watanabe, Nobuaki Watanabe, Misa Asakura, Seiji
241 Nakatani, Ayano Matsuoka, and Hiroki Miyata (Nihon Chouzai Co., Ltd.); Atsuko Ando, Atsuko
242 Matsumura, Yuya Meguro, Kuniko Nakabayashi, Yasuko Yamamura, Hiroko Okabe, Nagisa
243 Nakazawa, Sayaka Yamada, Miyuki Tanaka, Yasuko Funasaka, Miki Aoki, Masahiro Taniguchi,
244 Mariko Matsumoto, Airi Inoue, Tatsuyuki Hakuto, Junko Sugiyama, Setsuko Takada, Jumpei
245 Akai, Kenshiro Yamamoto, Masako Kato, Daishi Kobayashi, Eriko Imai, Ibuki Nagakubo, Ayuha

246 Kawai, Kie Saito, Aoyama Kyoko, Masanari Tsuji, Takashi Terakoshi, and Mayaka Honnami
 247 (Ain Pharmaciez Inc.); Toru Yamazaki, Masako Tomomatsu, Ayumi Isono, Azusa Mitsuno, Mayu
 248 Yoshino, Yuki Ochi, Masato Yoshida, Hirona Maehara, Tomomi Sasaki, Hiroko Ichihashi,
 249 Shinichi Miyashige, and Hiroki Tanaka (Kraft Inc.); Ayako Kaneko, Ko Hamura, Mariko Miyake,
 250 and Ritsuko Kusushima (Sogo Medical Co., Ltd.). We would also like to thank Editage
 251 (www.editage.com) for English language editing.

252

253

254 **References**

- 255 1. Kuwahara K, Honda T, Nakagawa T, Yamamoto S, Akter S, Hayashi T, Mizoue T.
 256 Associations of leisure-time, occupational, and commuting physical activity with risk of depressive
 257 symptoms among Japanese workers: a cohort study. *Int J Behav Nutr Phys Act.* 2015;12:119.
- 258 2. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health*
 259 *Econ Health Policy.* 2017;15(2):127-37
- 260 3. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X.
 261 Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life*
 262 *Res.* 2011;20(10):1727-36.
- 263 4. Ikeda S, Shiroywa T, Igarashi A, Noto S, Fukuda T, Saito S, Shimozuma K. Developing a
 264 Japanese version of the EQ-5D-5L value set. *J Natl Inst Public Health.* 2015;64(1):47-55.

- 265 5. Shiroiwa T, Ikeda S, Noto S, Igarashi A, Fukuda T, Saito S, Shimozuma K. Comparison of
266 Value Set Based on DCE and/or TTO Data: Scoring for EQ-5D-5L Health States in Japan. *Value*
267 *Health*. 2016;19(5):648-54.
- 268 6. Ikegami N, Campbell JC. Medical care in Japan. *N Engl J Med*. 1995;333(19):1295-9.
- 269 7. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F,
270 Briggs AH, Mauskopf J, Loder E, Force, I. Consolidated Health Economic Evaluation Reporting
271 Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic
272 Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*.
273 2013;16(2):231-50.
- 274 8. Fukuda T, Shiroiwa T, Ikeda S, Igarashi A, Akazawa M, Ishida H, Noto S, Saito S,
275 Sakamaki H, Shimozuma K, Takura T, Fukuda H, Moriwaki K, Tomita N, Kobayashi M. Guideline
276 for economic evaluation of healthcare technologies in Japan. *J Natl Inst Public Health*.
277 2013;62(6):625-40.
- 278 9. Hirose C, Fujii H, Iihara H, Ishihara M, Nawa-Nishigaki M, Kato-Hayashi H, Ohata K,
279 Sekiya K, Kitahara M, Matsushashi N, Takahashi T, Okuda K, Naruse M, Ishihara T, Sugiyama T,
280 Yoshida K, Suzuki A. Real-world data of the association between quality of life using the EuroQol 5
281 Dimension 5 Level utility value and adverse events for outpatient cancer chemotherapy. *Support*
282 *Care Cancer*. 2020;28(12):5943-52.

- 283 10. Tanaka K, Tachi T, Hori A, Osawa T, Nagaya K, Makino T, Inoue S, Yasuda M, Mizui T,
284 Nakada T, Goto C, Teramachi H. Cost utility analysis of pharmacist counseling care for breast
285 cancer chemotherapy outpatients. *Pharmazie*. 2019;74(7):439-42.
- 286 11. Fujikawa A, Suzue T, Jitsunari F, Hirao T. Evaluation of health-related quality of life using
287 EQ-5D in Takamatsu, Japan. *Environ Health Prev Med*. 2011;16(1):25-35. doi: 10.1007/s12199-010-
288 0162-1
- 289 12. Oransky I. Elisabeth Kübler-Ross. *Lancet*. 2004;364(9440):1120.

290

291 **Figure legends:**

292 Figure 1. Each value by 5-dimensions-5-levels according to age group

293

Figures

Figure 1

Each value by 5-dimensions-5-levels according to age group

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.Characteristicis.pdf](#)
- [Table2.HRQOL.pdf](#)