Lower effectiveness of intravenous steroid treatment for moderate-to-severe ulcerative colitis in hospitalised patients with older onset: A multicentre cohort study

Short title: Onset age and intravenous steroid treatment in UC

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Summary

Background: The increasing incidence of older-onset ulcerative colitis (UC), which has a higher risk of surgery, is a global health issue. However, data regarding intravenous steroid treatment, one of the important treatment options to avoid surgery, for older-onset UC is lacking.

Aims: To evaluate the association between onset age and effectiveness of intravenous steroids in UC.

Methods: This retrospective multicentre (27 facilities) cohort study included moderate-to-severe hospitalised UC patients who underwent their first intravenous steroids between April 2014 and July 2019. The primary outcome was clinical remission at day 30, using two-item patient-reported outcome scoring. The key secondary outcomes were risks of surgery and adverse events (death, infection, and venous thrombosis) within 90 days. A modified Poisson regression model was used for analysis.

Results: Overall, 467 UC patients (384 younger-onset and 83 older-onset) were enrolled. Clinical remission at day 30 was observed in 252 (65.6%) among younger-onset patients and 43 (51.8%) among older-onset patients (adjusted risk difference, -21.7% [95%CI, -36.1% to -7.2%]; adjusted risk ratio [ARR], 0.74 [95%CI, 0.59 to 0.93]). The risks of surgery and adverse events were higher in older-onset UC (20.5% vs. 3.1%; ARR, 8.92 [95%CI,

4.13 to 19.27], 25.3% vs. 9.1%; ARR, 2.19 [95%CI, 1.22 to 3.92], respectively). Four deaths occurred, all involving older-onset UC. The risks of infection and venous thrombosis were also higher in older-onset UC (18.1% vs. 8.6%, 7.2% vs. 0.5%, respectively).

Conclusions: Older-onset was associated with a lower effectiveness of intravenous steroids with higher risks of surgery and adverse events in UC.

Keywords

colitis, ulcerative; age of onset; steroids

Word count

4121 words

INTRODUCTION

The rising incidence of ulcerative colitis (UC) worldwide and the global increase in the aging population have led to a striking increase in older-onset UC[1-8]. UC is thought to be a disease that develops due to the complex interaction between genetic and environmental factors, as well as commensal gut microbiota, which causes a dysregulated immune response in the colon[9]. According to the differences in the respective contributions of these factors to the development of the disease depending on age, disease heterogeneity has been suggested between younger-onset UC and older-onset UC[6-8, 10-11].

It is debated whether there is a difference in natural history between younger-onset UC and older-onset UC. Some studies have reported a mild diseases course in older-onset UC with less frequent exposure to aggressive medical treatment[6-7], whereas other studies have reported that prognosis is not favourable in older-onset UC as compared with younger-onset UC[2, 10, 12-13]. A recent meta-analysis focusing on the age of onset revealed that older-onset UC requires a higher rate of surgery than younger-onset UC[13], and similar results were reported by recent nationwide cohort studies[10, 14-16]. The higher risk of surgery may be due to the difference in effectiveness of intravenous steroid treatment, which is one of the important treatment options to avoid surgery for a severe

course of UC[17-20]. However, data regarding the effectiveness and safety of intravenous steroid treatment for older-onset UC are lacking[16, 21-23].

In this multicentre cohort study, we investigated the effectiveness and safety of intravenous steroid treatment for moderate-to-severe UC in older-onset patients as compared to those presenting at a younger age.

METHODS

Study design and participants

This multicentre retrospective cohort study was conducted at 27 facilities in Japan, including both university and non-university hospitals. We used the data of consecutive UC patients presenting with a moderate or severe flare who required admission for their first intravenous steroid treatment from 1 April 2014 to 31 July 2019. All data were derived from the medical records of each participating institution. Ethical approval was obtained from all participating institutions. We used an opt-out approach for consent because this was a retrospective observational study, there was no risk to participants, and the collected data were managed in accordance with appropriate protection of privacy through data anonymization.

We included UC patients aged 18 years or older who were admitted for their first intravenous steroid treatment due to moderate or severe flare. Intravenous steroid treatment was defined as the use of prednisolone or its equivalent at a daily dose of ≥ 40 mg intravenously, and the dosing regimen was according to the guidelines[17-20].

We excluded patients who had already undergone colectomy or had a history of intravenous steroid treatment. Patients who received any of the following drugs for diseases other than UC were ineligible: systemic steroids, calcineurin inhibitors,

biological agents, or molecule inhibitors. We did not exclude patients who had a history of oral steroid use for UC.

Definition of younger-onset UC and older-onset UC

We categorised patients into younger-onset UC and older-onset UC according to age at the date of initial diagnosis. Although there is no universal cut-off age to classify UC by age of onset, a cut-off age of 60 years was the most widely used threshold in previous studies[5]. Thus, we defined younger-onset UC as UC initially diagnosed in patients under 60 years and older-onset UC as UC initially diagnosed in patients at 60 years or older.

Outcomes

We evaluated the differences in the effectiveness and safety of intravenous steroid treatment between younger-onset UC and older-onset UC.

The primary outcome was clinical remission at day 30. Day 30 was selected as an evaluation time point for assessing the effectiveness of intravenous steroid treatment for induction of remission based on previous studies[24-25] and the European Crohn's and Colitis Organisation guidelines[26]. If we were not able to obtain the data at day 30 because patients were discharged, the data within 1 week of day 30 was used. Clinical remission

was defined as a total score of ≤ 1 and a rectal bleeding subscore of 0 on the validated two-item patient-reported outcome (PRO2) scoring[27]. Patients who died, required surgery, or required another rescue treatment such as biological agents, molecule inhibitors, calcineurin inhibitors, or systemic steroids (re-induction) within 30 days were considered as failure of intravenous steroid treatment and were analysed as not in remission.

The secondary outcomes were clinical remission at day 3, clinical remission at day 7, clinical remission at day 90, steroid-free remission at day 90, surgery within 90 days, and adverse events (death, infection, and venous thrombosis) within 90 days. Day 3 and day 7 were selected as evaluation time points for assessing the initial response to steroids, and day 90 was selected for assessing steroid-dependency based on the guidelines[17-20, 26]. If we were not able to obtain the data at day 90 because patients were discharged, the data within 2 weeks of day 90 was used. Clinical remission was defined in accordance with the aforementioned definition. Patients who died, required surgery, or required another rescue treatment such as biological agents, molecule inhibitors, calcineurin inhibitors, or systemic steroids (re-induction) within 90 days were considered as failure of intravenous steroid treatment and were analysed as not in remission. Adverse events of infection were defined as requiring antimicrobial drugs or surgical

procedures such as debridement for infection control[28]. Venous thrombosis was defined following a record of the definitive diagnosis in the medical records.

Covariates

Data on sex, disease duration, disease extent, disease severity, comorbidity, concomitant drug use, and smoking status at the date of the initiation of intravenous steroid treatment were obtained. Disease extent was classified into proctitis, left-sided colitis, and extensive colitis[29]. Disease severity was assessed according to the Truelove and Witts criteria[30]. Regarding comorbidity, we used the Charlson comorbidity index (CCI)[31-32] to assess the major comorbid disease burden, and categorised the CCI into a score of 0 and a score of ≥ 1[33]. We included the following concomitant drugs in covariates: 5-aminosalicylic acid, immunomodulators (azathioprine and mercaptopurine hydrate), non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs, and anticoagulant drugs. The use of these drugs was determined by recorded use at the initiation of intravenous steroid treatment.

Statistical analysis

Baseline characteristics of patients were described using means with standard

deviations or medians with interquartile ranges for continuous data and absolute numbers with percentages for categorical data. A modified Poisson regression model[34-35] was used to estimate risk differences (RDs) and risk ratios (RRs) to evaluate the difference in the clinical outcomes between younger-onset UC and older-onset UC. Multivariable analysis was adjusted for sex, disease duration, disease extent, disease severity, comorbidity, use of the concomitant drugs, and smoking status. These variables were selected based on the clinical perspective and variables identified in previous studies as potential confounders[8]. We conducted four sensitivity analyses to confirm the robustness of the main analyses of the primary outcome. First, we changed the cut-off for age of onset from 60 years to 50 years and 70 years. Second, we changed the covariates by including C-reactive protein (CRP) values in the multivariable analysis. Third, we changed the covariates by including body weights in the multivariable analysis. Fourth, we changed the definition of the primary outcome not to include initiation of rescue treatment as failure, and evaluated the 30-day colectomy rate because rescue treatment is likely to reduce the rate of colectomy. Kaplan-Meier plots and the Cox proportional hazards regression model were used for analysis to compare the 30-day colectomy rate between patients with younger-onset UC and older-onset UC. We used a log-rank test to compare the curves of the Kaplan-Meier plots. Moreover, we conducted

a stratified analysis that we analysed the data after stratification of intravenous steroid dose into ≥ 60 mg/day or < 60 mg/day with regards to the primary outcome and adverse events[19]. We also assessed the proportion of clinical remission at day 30 by age of onset, grouped by every 10 years of age. Among the adverse events, we describe the details of death and infection.

We performed additional analyses to differentiate the influence of age of onset on effectiveness of intravenous steroid treatment from those of age itself, meaning whether older-onset of the disease or older age at initiation of treatment is associated with effectiveness of intravenous steroid treatment. Thus, patients treated with intravenous steroids in older age were divided into two groups according to age of onset: older individuals with younger-onset UC and older individuals with older-onset UC. We then evaluated the differences in the clinical outcomes among older individuals with younger-onset UC, older individuals with older-onset UC, and young UC (age at initiation of intravenous steroids < 60 years).

Multiple imputation was performed to account for missing covariates by 20 imputed datasets based on all observed predictive information, including outcome[36-37]. We reported 95% two-sided confidence intervals (CIs) as an informal measure of uncertainty and avoided using terms such as statistically significant and a like according

to the recommendation of the American Statistical Association[38]. Analyses were performed using Stata version 16.0 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics

A total of 480 patients with UC who were admitted for their first intravenous steroid treatment due to moderate or severe flare met the eligibility criteria at the 27 facilities. Of those, 13 (2.7%) patients were excluded from the analyses because the study outcomes were not obtained due to the following reasons: hospital transfers shortly after initiation of the treatment (9 patients) and loss to follow-up for personal reasons (4 patients) (Figure 1). Thus, 467 patients were included in the analyses, and their baseline characteristics are presented in Table 1.

We identified 384 (82.2%) younger-onset UC patients and 83 (17.8%) older-onset UC patients. The median age of onset was 32 years in younger-onset UC and 68 years in older-onset UC. Disease duration was shorter in older-onset UC than younger-onset UC (2 vs. 18 months). Acute severe cases were 43.2% (166/384) in younger-onset UC and 44.6% (37/83) in older-onset UC according to Truelove and Witts criteria. Comorbidities, smoking status, and antiplatelet drug usage were more common in older-onset UC than younger-onset UC (42.2% vs. 9.6%, 40.0% vs. 25.3%, 6.0% vs. 1.6%, respectively), but immunomodulator drug usage was less common (1.2% vs. 7.3%). The proportions of biologics used after initiation of intravenous steroid treatment were

13.8% (53/384) and 9.6% (8/83) in those with younger-onset UC and older-onset UC, respectively. Among these patients who used biologics, the interval from initiation of intravenous steroid treatment to initiation of biologics was not substantially different between those with younger-onset UC and those with older-onset UC with a median of 13 (7 to 19) days and 17.5 (8 to 48) days, respectively.

Clinical outcomes at day 30 (primary outcome)

In total, 295 (63.2%) patients achieved clinical remission at day 30, and the proportion of clinical remission tended to be decreased among older-onset UC patients (Figure 2). Clinical remission at day 30 was observed in 252 (65.6%) younger-onset UC patients and 43 (51.8%) older-onset UC patients (crude RD, -13.8% [95% CI, -25.6% to -2.1%], P = 0.021; crude RR, 0.79 [95% CI, 0.63 to 0.98], P = 0.035) (Table 2). Multivariable analysis showed that clinical remission at day 30 was achieved in fewer patients with older-onset UC than in those with younger-onset UC (adjusted RD, -21.7% [95% CI, -36.1% to -7.2%], P = 0.003; adjusted RR, 0.74 [95% CI, 0.59 to 0.93], P = 0.009).

In the sensitivity analyses, the adjusted RRs of clinical remission at day 30 were 0.80 (95% CI, 0.67 to 0.96) (P = 0.018) and 0.63 (95% CI, 0.42 to 0.94) (P = 0.026) when the cut-off age was defined as 50 years and 70 years, respectively (Supplementary Table

S1). The adjusted RR of clinical remission at day 30 was 0.74 (95% CI, 0.59 to 0.93) (P = 0.009) when the covariates were changed by including CRP values. The adjusted RR of clinical remission at day 30 was also 0.74 (95% CI, 0.59 to 0.93) (P = 0.009) when the covariates were changed by including body weights. Kaplan-Meier plots of colectomy rate were shown in Figure 3. The incidence of 30-day colectomy was 1.8% (7/384) in the younger-onset UC and 15.7% (13/83) in the older-onset UC, yielding higher 30-day colectomy rate in patients with older-onset UC (crude hazard ratio, 9.47 [3.78 to 23.8], P < 0.001; adjusted hazard ratio, 16.7 [95% CI, 5.71 to 48.8], P < 0.001) when initiation of rescue treatment as not failure. Moreover, older-onset UC had a poorer outcome compared to younger-onset UC even from the intravenous steroid dose-stratified analysis as shown in Supplementary Table S2.

Clinical outcomes at day 3 and day 7

The total number of patients who achieved clinical remission at day 3 and day 7 were 68 (14.6%) and 163 (34.9%), respectively. Initial response to intravenous steroid treatment was poorer in older-onset UC than in younger-onset UC both at day 3 (10.8% vs. 15.4%; adjusted RR, 0.64 [95% CI, 0.32 to 1.28], P = 0.206) and day 7 (26.5% vs. 36.7%; adjusted RR, 0.69 [95% CI, 0.47 to 1.02], P = 0.062); however, these differences were not

significant (Table 2).

Clinical outcomes at day 90

The total number of patients who achieved clinical remission at day 90 and steroid-free remission at day 90 were 287 (61.5%) and 157 (33.6%), respectively. Clinical remission at day 90 was observed in 243 (63.3%) younger-onset UC patients and 44 (53.0%) older-onset UC patients (crude RR, 0.84 [95% CI, 0.67 to 1.04], P = 0.109). Multivariable analysis showed that remission was achieved in fewer patients with older-onset UC than in those with younger-onset UC (adjusted RR, 0.81 [95% CI, 0.64 to 1.01], P = 0.065); however, this difference was not significant (Table 2). Steroid-free remission at day 90 was observed in 128 (33.3%) younger-onset UC patients and 29 (34.9%) older-onset UC patients (crude RR, 1.05 [95% CI, 0.76 to 1.45], P = 0.777). Multivariable analysis showed that this achievement was similar in both groups (adjusted RR, 1.07 [95% CI, 0.76 to 1.50], P = 0.719) (Table 2).

Overall, 29 (6.2%) patients required surgery within 90 days. Kaplan-Meier plots of colectomy rate are shown in Figure 3. Twelve (3.1%) younger-onset UC patients and 17 (20.5%) older-onset UC patients required surgery within 90 days (crude RR, 6.55 [95% CI, 3.25 to 13.21], P < 0.001). The risk for surgery was higher in older-onset UC according

to multivariable analysis (adjusted RR, 8.92 [95% CI, 4.13 to 19.27], P < 0.001) (Table 2). This higher risk of surgery in patients with older-onset UC was seen even though the proportions of biologics used after initiation of intravenous steroid treatment were similar between the two groups.

Overall, 56 (12.0%) patients experienced adverse events. More specifically, adverse events were observed in 35 (9.1%) younger-onset UC patients and 21 (25.3%) older-onset UC patients (crude RR, 2.78 [95% CI, 1.71 to 4.52], P < 0.001). The risk of adverse events was higher in older-onset UC according to multivariable analysis (adjusted RR, 2.19 [95% CI, 1.22 to 3.92], P = 0.008) (Table 2). In a stratified analysis of the dose of intravenous steroids, there was a higher incidence of adverse events in older-onset UC patients who used ≥ 60 mg/day (Supplementary Table S3). There were 4 (0.9%) deaths, 48 (10.3%) infections, and 8 (1.7%) venous thromboses in this study, and older-onset UC patients had a higher risk of all of these events (Table 2). The causes of death were pneumocystis pneumonia, bacterial pneumonia, stroke, and multiple organ failure due to uncontrolled UC, all of which were observed in older-onset UC.

Comparison of young UC, older individuals with younger-onset UC, and older individuals with older-onset UC

We identified 351 (75.2%) young UC cases, 33 (7.1%) older individuals with younger-onset UC, and 83 (17.8%) older individuals with older-onset UC. Their baseline characteristics are shown in Table 3. Using young UC as a reference, the achievement of clinical remission at day 30 was similar in older individuals with younger-onset UC (adjusted RD, -3.5% [95% CI, -22.6% to 15.6%], P = 0.718; adjusted RR, 0.91 [95% CI, 0.68 to 1.23], P = 0.548), whereas it was lower in older individuals with older-onset UC (adjusted RD, -22.0% [95% CI, -36.6% to -7.4%], P = 0.003; adjusted RR, 0.73 [95% CI, 0.58 to 0.92], P = 0.008) (Table 4).

Clinical remission at day 3 and day 7 showed similar results to clinical remission at day 30. Compared with young UC, older individuals with older-onset UC had poorer outcomes, while older individuals with younger-onset UC did not (Table 4).

Compared with young UC, achievement of clinical remission at day 90 was lower in older individuals with younger-onset UC and in older individuals with older-onset UC, but the achievement of steroid-free remission at day 90 was lower only in older individuals with younger-onset UC (Table 4). The proportion of patients who discontinued steroids by day 90 was 53.6% (120/224) in young UC, 42.1% (8/19) in older individuals with younger-onset UC, and 65.9% (29/44) in older individuals with older-onset UC. We found that the age of onset, rather than age at initiation of treatment, was

associated with a higher risk of surgery within 90 days (adjusted RR, 9.25 [95% CI, 4.24 to 20.19], P < 0.001) as well as of adverse events within 90 days (adjusted RR, 2.32 [95% CI, 1.29 to 4.18], P = 0.005) (Table 4 and Supplementary Table S4).

DISCUSSION

In this multicentre cohort study, older-onset UC patients had a lower effectiveness of intravenous steroid treatment, with higher risks of surgery and adverse events, than younger-onset UC patients. Moreover, we demonstrated that the treatment outcomes were associated with age of onset rather than with age at initiation of the treatment in older UC patients, based on an analysis of older individuals with younger-onset UC and older individuals with older-onset UC.

Our results were consistent with the findings of a recent meta-analysis[13], which showed a poor prognosis with a higher risk of surgery in cases with older-onset UC than in those with younger-onset UC. No previous study has specifically assessed the effectiveness and safety of intravenous steroid treatment for patients with older-onset UC, and our findings clearly suggests that one of the reasons for the poor prognosis in patients with older-onset UC is the lower effectiveness of intravenous steroid treatment, which is one of the important treatment options for a severe course of UC. A few previous studies have examined the association between older age and effectiveness of steroid treatment in UC[16, 21-23], but no clear association has been reported; this is different from the present results. Possible explanations for the discrepancy in the results may have occurred because previous studies did not separate oral and

intravenous administration in their evaluation[16, 21-22] or because they did not differentiate older UC patients into younger-onset and older-onset[23]. In our study, we focused on UC patients who underwent intravenous steroid treatment, and we clearly separated older UC patients according to age of onset. As a result, the effectiveness of intravenous steroid treatment for induction of remission was similar in older individuals with younger-onset UC, but was lower with a high risk of surgery in older individuals with older-onset UC, compared with young UC.

The outcome of intravenous steroid treatment was worse in patients with older-onset UC for some possible reasons. First, disease heterogeneity due to differences in the respective contributions of genetic susceptibility, environmental factors, and commensal gut microbiota, depending on age of onset, suggests differences in dysregulated immune responses[8], which may lead to different phenotypes of disease or responses to intravenous steroid treatment. The lower effectiveness of intravenous steroid treatment in older-onset UC may indicate a phenotype with a biologically more severe course of disease that cannot be explained by factors that were considered as variables in this study[8,10,13-14]. Another possible explanation is that, in the dysregulated immune response in older-onset UC, there may be a mechanism by which immunosuppression with intravenous steroid treatment is not effective. Unfortunately,

we did not have data on regarding differences in genetic susceptibility, environmental factors, and commensal gut microbiota in this study. Thus, further research is needed to evaluate the influence of these factors on disease phenotype and on the response to intravenous steroid treatment. Second, the outcome of older-onset UC may have been worse because disease activity was not evaluated properly via endoscopy, which could have led to patients with older-onset UC being treated less aggressively with rescue treatment. Third, there may have been a higher risk of surgery in patients with older-onset UC due to the co-existence of cytomegalovirus colitis, diverticular colitis, or ischaemia. However, the data on histological examination for cases of colectomy is lacking in this study, and further studies are required to evaluate risk of surgery from co-existent diseases.

The present study showed that older individuals with older-onset UC successfully achieved steroid-free remission at day 90 rather than older individuals with younger-onset UC, which was different from the results of clinical remission at day 30. This may indicate that, in older individuals with older-onset UC, inducing remission is difficult but maintaining remission after induction is successful. This finding was consistent with a previous study that showed that maintenance treatment drugs such as immunomodulators are more effective and can successfully maintain steroid-free clinical

remission in older-onset UC, compared with younger-onset UC[21]. However, our results may have been caused by differences in clinical practices such as steroid tapering schedules or steroid-sparing maintenance drug usage. In fact, the proportion of patients who discontinued steroids by day 90 was higher in older-onset UC than in younger-onset UC, suggesting that steroids may have been tapered as early as possible due to concerns of adverse events in older-onset UC patients. This may be one reason why the proportion of steroid-free remission in younger-onset UC was not different from that in patients with older-onset UC. Further research regarding steroid tapering schedules and maintenance therapy after induced remission for older UC patients is needed.

There was a higher risk of adverse events in older-onset UC than younger-onset UC; this finding was consistent even when we performed additional analyses with older individuals with older-onset UC and older individuals with younger-onset UC. Among the adverse events, death and venous thrombosis were almost exclusively observed in older-onset UC, which may support a complicated course of the disease among these patients. Moreover, there was a higher incidence of adverse events in older-onset UC patients who used higher doses of intravenous steroids[39]. Our findings that the effectiveness and safety of intravenous steroid treatment depended on the age of onset could assist in better management of disease by allowing an appropriate treatment response

prediction and monitoring with consideration of different effects of the treatment. More evidence regarding medical treatment other than intravenous steroid treatment based on age of onset may also be required.

Our study had some limitations. First, unmeasured confounders, particularly in confounding by indication, may have had some influence on the observed high risk of surgery in older-onset UC. The risk of surgery in the present study was higher than that reported in a previous meta-analysis (odds ratio, 1.36 [95% CI, 1.18 to 1.57])[13], which may be partly because older patients with UC refractory to intravenous steroid treatment has undergone surgery without going through salvage therapies due to concerns of delay in surgery. Limiting the study participants to moderate-to-severe UC patients who required intravenous steroid treatment may have also contributed to the observed higher risk of surgery. Second, the possibility of other unmeasured confounders such as concomitant drugs (e.g., proton pump inhibitors and sartans) and detailed nutritional status (e.g., serum albumin) are also an issue of concern, although we considered the most well-known potential confounders in the analysis. Third, treatment effect was evaluated by scoring only based on symptoms rather than on objective measures such as endoscopy and histology due to the retrospective nature of the study. The lack of these data is an important limitation because there may have been

discrepancies between PRO2 score and endoscopic/histologic findings, and it is unclear whether disease activity was evaluated accurately at proper timings or whether co-existent diseases such as cytomegalovirus colitis, diverticular colitis, or ischaemia affected outcomes. Further prospective research may be required to evaluate the effect of treatment using such measures. Fourth, we do not have the data regarding access to healthcare and thus cannot evaluate whether a delay in diagnosis of older-onset UC led to the worse outcome. However, the disease severity at time of initiation of intravenous steroid treatment was similar between patients with older-onset UC and those with younger-onset UC and was adjusted as covariates in the analysis of this study.

In conclusion, older-onset UC showed a lower effectiveness of intravenous steroid treatment with higher risks of surgery and of adverse events than younger-onset UC. Further research is warranted to establish the optimal treatment strategies for moderate-to-severe older-onset UC.

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Authorship statement

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Authorship contributions: Okabayashi, S., Yamazaki, H., Tominaga, K., Miura, M., Sagami, S., Andoh, A., Yamamoto, Y., Hibi, T., and Kobayashi, T. conceived and supervised the study. Okabayashi, S., Yamazaki, H., Tominaga, K., Miura, M., Sagami, S., Yamamoto, Y., and Kobayashi, T. contributed to the study design. Okabayashi, S., Tominaga, K., Miura, M., Sagami, S., Matsuoka, K., Yamaguchi, Y., Noake, T., Ozeki, K., Miyazaki, R., Kamano, T., Fukuda, T., Yoshioka, K., Ando, K., Fukuzawa, M., Takahashi, S., Hayasaka, J., Yokoyama, K., Takenaka, K., Saegusa, Y., Ogashiwa, T., Honzawa, Y., Tani, M., Nanjo, S., Oouchi, S., Hirayama, D., Sawada, T., Negoro, Y., and Moriya, K. contributed to extraction of the data. Okabayashi, S., Yamazaki, H., and Yamamoto, Y. contributed to statistical analysis and

interpretation of the findings. Okabayashi, S., Yamazaki, H., Tominaga, K., Miura, M., Sagami, S., Yamamoto, Y., and Kobayashi, T. contributed to drafting the manuscript, and all authors reviewed and approved the final version of the article, including the authorship list.

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All authors have no conflicts of interest directly associated with this study. SS has served as a speaker for AbbVie, Takeda Pharmaceutical, Zeria Pharmaceutical and an endowed chair from AbbVie, JIMRO, Zeria Pharmaceutical, Kyorin Pharmaceutical, Mochida Pharmaceutical, EA Pharma. KM has received lecture fees from Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Abbvie Inc., EA Pharma Co., Ltd., Pfizer Inc., Mochida Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., ZERIA Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Alfresa Pharma Corporation, JIMRO Co., Ltd., Miyarisan Pharmaceutical Co., Ltd; has

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Data Availability Statements

The data are not publicly available due to privacy or ethical restrictions.

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46-54.
2. Shi HY, Chan FK, Leung WK, et al. Natural History of Elderly-onset Ulcerative Colitis: Results from a Territory-wide Inflammatory Bowel Disease Registry. J Crohns Colitis 2016;10:176-85.
3. Song EM, Lee HS, Park SH, et al. Clinical characteristics and long-term prognosis of elderly onset ulcerative colitis. J Gastroenterol Hepatol 2018;33:172-9.
4. Takahashi H, Matsui T, Hisabe T, et al. Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation. J Gastroenterol Hepatol 2014;29:1603-8.
5. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. J Crohns Colitis 2017;11:263-73.
6. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut 2014;63:423-32.
7. Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: results from a population-based study in Western Hungary, 1977-2008. J Crohns Colitis 2011;5:5-

13.

8. Ruel J, Ruane D, Mehandru S, Gower-Rousseau C, Colombel JF. IBD across the age spectrum: is it the same disease? Nat Rev Gastroenterol Hepatol 2014;11:88-98.
9. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. Nat Rev Dis Primers 2020;6:74.
10. Komoto S, Higashiyama M, Watanabe C, et al. Clinical differences between elderly-onset ulcerative colitis and non-elderly-onset ulcerative colitis: A nationwide survey data in Japan. J Gastroenterol Hepatol 2018;33:1839-43.
11. Duricova D, Burisch J, Jess T, Gower-Rousseau C, Lakatos PL; ECCO-EpiCom. Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature. J Crohns Colitis 2014;8:1351-61.
12. Olen O, Askling J, Sachs MC, et al. Mortality in adult-onset and elderly-onset IBD: a nationwide register-based cohort study 1964-2014. Gut 2020;69:453-61.
13. Ananthakrishnan AN, Shi HY, Tang W, et al. Systematic Review and Meta-analysis: Phenotype and Clinical Outcomes of Older-onset Inflammatory Bowel Disease. J Crohns Colitis 2016;10:1224-36.
14. Nguyen GC, Bernstein CN, Benchimol EI. Risk of Surgery and Mortality in Elderly-onset Inflammatory Bowel Disease: A Population-based Cohort Study. Inflamm

Bowel Dis 2017;23:218-23.

15. Lin WC, Tung CC, Lin HH, et al. Elderly Adults with Late-Onset Ulcerative Colitis Tend to Have Atypical, Milder Initial Clinical Presentations but Higher Surgical Rates and Mortality: A Taiwan Society of Inflammatory Bowel Disease Study. J Am Geriatr Soc 2016;64:e95-e7.
16. Fries W, Viola A, Manetti N, et al. Disease patterns in late-onset ulcerative colitis: Results from the IG-IBD "AGED study". Dig Liver Dis 2017;49:17-23.
17. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol 2019;114:384-413.
18. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology 2020;158:1450-61.
19. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis 2017;11:769-84.
20. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol 2018;53:305-53.
21. Ha CY, Newberry RD, Stone CD, Ciorba MA. Patients with late-adult-onset ulcerative

colitis have better outcomes than those with early onset disease. Clin Gastroenterol Hepatol 2010;8:682-7e1.

22. Duricova D, Pariente B, Sarter H, et al. Impact of age at diagnosis on natural history of patients with elderly-onset ulcerative colitis: A French population-based study. Dig Liver Dis 2018;50:903-9.
23. Weber NK, Bruining DH, Loftus EV Jr, et al. Comparative outcomes of younger and older hospitalized patients with inflammatory bowel disease treated with corticosteroids. Inflamm Bowel Dis 2013;19:2644-51.
24. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255-60.
25. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5:103-10.
26. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: difinitions and diagnosis. J Crohns Colitis 2012;6:965-90.
27. Jairath V, Khanna R, Zou GY, et al. Development of interim patient-reported outcome

measures for the assessment of ulcerative colitis disease activity in clinical trials. Aliment Pharmacol Ther 2015;42:1200-10.

28. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929-36.
29. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-53.
30. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041-8.
31. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
32. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-51.
33. Lobatón T, Ferrante M, Rutgeerts P, Ballet V, Van Assche G, Vermeire S. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. Aliment Pharmacol Ther 2015;42:441-51.
34. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in

cohort studies of common outcomes. JAMA 1998;280:1690-1.

35. Holmberg MJ, Andersen LW. Estimating Risk Ratios and Risk Differences: Alternatives to Odds Ratios. JAMA 2020;324:1098-9.

36. Newgard CD, Haukoos JS. Advanced statistics: missing data in clinical research--part 2: multiple imputation. Acad Emerg Med 2007;14:669-78.

37. Aloisio KM, Swanson SA, Micali N, Field A, Horton NJ. Analysis of partially observed clustered data using generalized estimating equations and multiple imputation. Stata J 2014;14:863-83.

38. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. Am Stat 2016;70:129-33.

39. Baron JH, Connell AM, Kanaghinis TG, et al. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. Br Med J 1962;2:441-3.

Figure legends

Figure 1. Study flow chart and numbers of patients.

Figure 2. Proportion of patients with clinical remission at day 30 according to age of onset, grouped by every 10 years of age.

Figure 3. Kaplan-Meier plots of colectomy rate.

Table 1. Baseline characteristics of the study participants

	Younger-onset UC (n=384)	Older-onset UC (n=83)
Male (n, %)	234 (60.9)	50 (60.2)
Body weight (mean in kg, SD)	58.0 (12.6)	56.1 (10.6)
Age of onset (median in years, IQR)	32 (22–44)	68 (63–72)
Disease duration (median in months, IQR)	18 (1–80.5)	2 (0–28)
0 ≤ duration < 1 month (n, %)	54 (14.1)	26 (31.3)
1 ≤ duration < 12 months (n, %)	117 (30.5)	31 (37.4)
12 months ≤ duration (n, %)	213 (55.5)	26 (31.3)
Disease extent		
Proctitis (n, %)	3 (0.8)	0 (0)
Left-sided colitis (n, %)	65 (16.9)	20 (24.1)
Extensive colitis (n, %)	316 (82.3)	63 (75.9)
Disease severity (Truelove and Witts criteria)		
Moderately severe (n, %)	218 (56.8)	46 (55.4)
Acute severe (n, %)	166 (43.2)	37 (44.6)
PRO2 total score (median, IQR)	5 (4–6)	5 (3–6)
Stool frequency subscore (median, IQR)	3 (3–3)	3 (2–3)
Rectal bleeding subscore (median, IQR)	2 (1–3)	2 (1–3)
Concomitant drugs		
5-aminosalicylic acid (n, %)	314 (81.8)	64 (77.1)
Immunomodulators (n, %)	28 (7.3)	1 (1.2)
NSAIDs (n, %)	20 (5.2)	5 (6.0)
Anticoagulant drugs (n, %)	5 (1.3)	3 (3.6)
Antiplatelet drugs (n, %)	6 (1.6)	5 (6.0)
History of oral steroid use (n, %)	139 (36.4)	17 (20.7)
History of biologic use (n, %)	8 (2.1)	3 (3.6)
Charlson comorbidity index ≥ 1 (n, %)	37 (9.6)	35 (42.2)
Current smoker (n, %)	92 (25.3)	32 (40.0)
CRP (median in mg/L, IQR)	63 (21–125)	71 (28–121)
Initial dose of steroid (mean in mg, SD)	54.1 (11.1)	51.7 (10.7)
University hospital (n, %)	313 (81.5)	64 (77.1)

UC denotes ulcerative colitis; IQR, interquartile range; SD, standard deviation; PRO2, two-item patient-reported outcome; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein.

Missing data on current smoker in 23 (4.9%) participants, history of oral steroids use in 3 (0.6%) participants, and CRP in 2 (0.4%)

participants, and body weight in 4 (0.9%) participants.

Table 2. Summary of primary and secondary outcomes of younger-onset UC and older-onset UC

	Younger-onset UC (n=384)	Older-onset UC (n=83)	Crude RR (95% CI)	Adjusted† RR (95% CI)
Primary outcome				
Clinical remission at day 30 (n, %)	252 (65.6)	43 (51.8)	0.79 (0.63–0.98)	0.74 (0.59–0.93)
Secondary outcomes				
Clinical remission at day 3 (n, %)	59 (15.4)	9 (10.8)	0.71 (0.36–1.37)	0.64 (0.32–1.28)
Clinical remission at day 7 (n, %)	141 (36.7)	22 (26.5)	0.72 (0.49–1.06)	0.69 (0.47–1.02)
Clinical remission at day 90 (n, %)	243 (63.3)	44 (53.0)	0.84 (0.67–1.04)	0.81 (0.64–1.01)
Steroid-free remission at day 90 (n, %)	128 (33.3)	29 (34.9)	1.05 (0.76–1.45)	1.07 (0.76–1.50)
Required surgery within 90 days (n, %)	12 (3.1)	17 (20.5)	6.55 (3.25–13.21)	8.92 (4.13–19.27)
Adverse events within 90 days (n, %)	35 (9.1)	21 (25.3)	2.78 (1.71–4.52)	2.19 (1.22–3.92)
Death‡ (n, %)	0 (0)	4 (4.8)		
Infection (n, %)	33 (8.6)	15 (18.1)		
Venous thrombosis (n, %)	2 (0.5)	6 (7.2)		

UC denotes ulcerative colitis; RR, risk ratio; CI, confidence interval.

†Adjusted for sex, disease duration, disease extent, disease severity, comorbidity, use of concomitant drugs (5-aminosalicylic acid, immunomodulators, non-steroidal anti-inflammatory drugs, anticoagulant drugs, and antiplatelet drugs), and smoking status.

‡ The causes of death: pneumocystis pneumonia, bacterial pneumonia, stroke, and multiple organ failure due to uncontrolled UC.

Table 3. Baseline characteristics of young UC, older individuals with younger-onset UC, and older individuals with older-onset UC

	Young (< 60 years)	Older individuals (≥ 60 years)	
	Younger-onset UC (n=351)	Younger-onset UC (n=33)	Older-onset UC (n=83)
Male (n, %)	216 (61.5)	18 (54.6)	50 (60.2)
Body weight (mean in kg, SD)	58.4 (12.7)	54.7 (10.8)	56.1 (10.6)
Age of onset (median in years, IQR)	30 (21–42)	52 (47–58)	68 (63–72)
Disease duration (median in months, IQR)	13 (1–65)	150 (48–259)	2 (0–28)
0 ≤ duration < 1 month (n, %)	54 (15.4)	0 (0)	26 (31.3)
1 ≤ duration < 12 months (n, %)	114 (32.5)	3 (9.1)	31 (37.4)
12 months ≤ duration (n, %)	183 (52.1)	30 (90.9)	26 (31.3)
Disease extent			
Proctitis (n, %)	3 (0.9)	0 (0)	0 (0)
Left-sided colitis (n, %)	55 (15.7)	10 (30.3)	20 (24.1)
Extensive colitis (n, %)	293 (83.5)	23 (69.7)	63 (75.9)
Disease severity (Truelove and Witts criteria)			
Moderately severe (n, %)	195 (55.6)	23 (69.7)	46 (55.4)
Acute severe (n, %)	156 (44.4)	10 (30.3)	37 (44.6)
PRO2 total score (median, IQR)	5 (4–6)	5 (4–5)	5 (3–6)
Stool frequency subscore (median, IQR)	3 (3–3)	3 (3–3)	3 (2–3)
Rectal bleeding subscore (median, IQR)	2 (2–3)	2 (1–3)	2 (1–3)
Concomitant drugs			
5-aminosalicylic acid (n, %)	286 (81.5)	28 (84.9)	64 (77.1)
Immunomodulators (n, %)	27 (7.7)	1 (3.0)	1 (1.2)
NSAIDs (n, %)	17 (4.8)	3 (9.1)	5 (6.0)
Anticoagulant drugs (n, %)	3 (0.9)	2 (6.1)	3 (3.6)
Antiplatelet drugs (n, %)	6 (1.7)	0 (0)	5 (6.0)
History of oral steroid use (n, %)	122 (35.0)	17 (51.5)	17 (20.7)
History of biologic use (n, %)	8 (2.3)	0 (0)	3 (3.6)
Charlson comorbidity index ≥ 1 (n, %)	27 (7.7)	10 (30.3)	35 (42.2)
Current smoker (n, %)	86 (25.8)	6 (20.0)	32 (40.0)
CRP (median in mg/L, IQR)	65 (21–125)	61 (22–130)	71 (28–121)
Initial dose of steroid (mean in mg, SD)	54.4 (11.2)	51.2 (9.6)	51.7 (10.7)

University hospital (n, %)	290 (82.6)	23 (69.7)	64 (77.1)

UC denotes ulcerative colitis; IQR, interquartile range; SD, standard deviation; PRO2, two-item patient-reported outcome; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein.

Young UC was defined as age at initiation of intravenous steroids < 60 years and age of disease onset < 60 years.

Older individuals with younger-onset UC was defined as age at initiation of intravenous steroids ≥ 60 years and age of disease onset < 60 years.

Older individuals with older-onset UC was defined as age at initiation of intravenous steroids ≥ 60 years and age of disease onset ≥ 60 years.

Missing data on current smoker in 23 (4.9%) participants, history of oral steroids use in 3 (0.6%) participants, and CRP in 2 (0.4%) participants, and body weight in 4 (0.9%) participants.

Table 4. Differences in clinical outcomes among young UC, older individuals with younger-onset UC, and older individuals with older-onset UC

	Young (< 60 years)	Older individuals (≥ 60 years)	
	Younger-onset UC (n=351)	Younger-onset UC (n=33)	Older-onset UC (n=83)
Primary outcome			
Clinical remission at day 30			
Number of events (n, %)	230 (65.5)	22 (66.7)	43 (51.8)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	0.91 (0.68–1.23)	0.73 (0.58–0.92)
Secondary outcomes			
Clinical remission at day 3			
Number of events (n, %)	52 (14.8)	7 (21.2)	9 (10.8)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	0.97 (0.42–2.20)	0.64 (0.32–1.27)
Clinical remission at day 7			
Number of events (n, %)	126 (35.9)	15 (45.5)	22 (26.5)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	1.14 (0.72–1.81)	0.70 (0.48–1.04)
Clinical remission at day 90			
Number of events (n, %)	224 (63.8)	19 (57.6)	44 (53.0)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	0.73 (0.52–1.02)	0.78 (0.62–0.99)
Steroid-free remission at day 90			
Number of events (n, %)	120 (34.2)	8 (24.2)	29 (34.9)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	0.47 (0.23–0.94)	1.01 (0.71–1.42)
Required surgery within 90 days			
Number of events (n, %)	11 (3.1)	1 (3.0)	17 (20.5)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	1.93 (0.25–14.95)	9.25 (4.24–20.19)
Adverse events within 90 days			
Number of events (n, %)	30 (8.6)	5 (15.2)	21 (25.3)
Death (n, %)	0 (0)	0 (0)	4 (4.8)
Infection (n, %)	28 (8.0)	5 (15.2)	15 (18.1)
Venous thrombosis (n, %)	2 (0.6)	0 (0)	6 (7.2)
Risk ratio (adjusted†, 95% CI)	1 [Reference]	1.62 (0.68–3.88)	2.32 (1.29–4.18)

UC denotes ulcerative colitis; CI, confidence interval.

†Adjusted for sex, disease duration, disease extent, disease severity, comorbidity, use of concomitant drugs (5-aminosalicylic acid, immunomodulators, non-steroidal anti-inflammatory drugs, anticoagulant drugs, and antiplatelet drugs), and smoking status.

Appendix 1.

IBD Terakoya Group Collaborators

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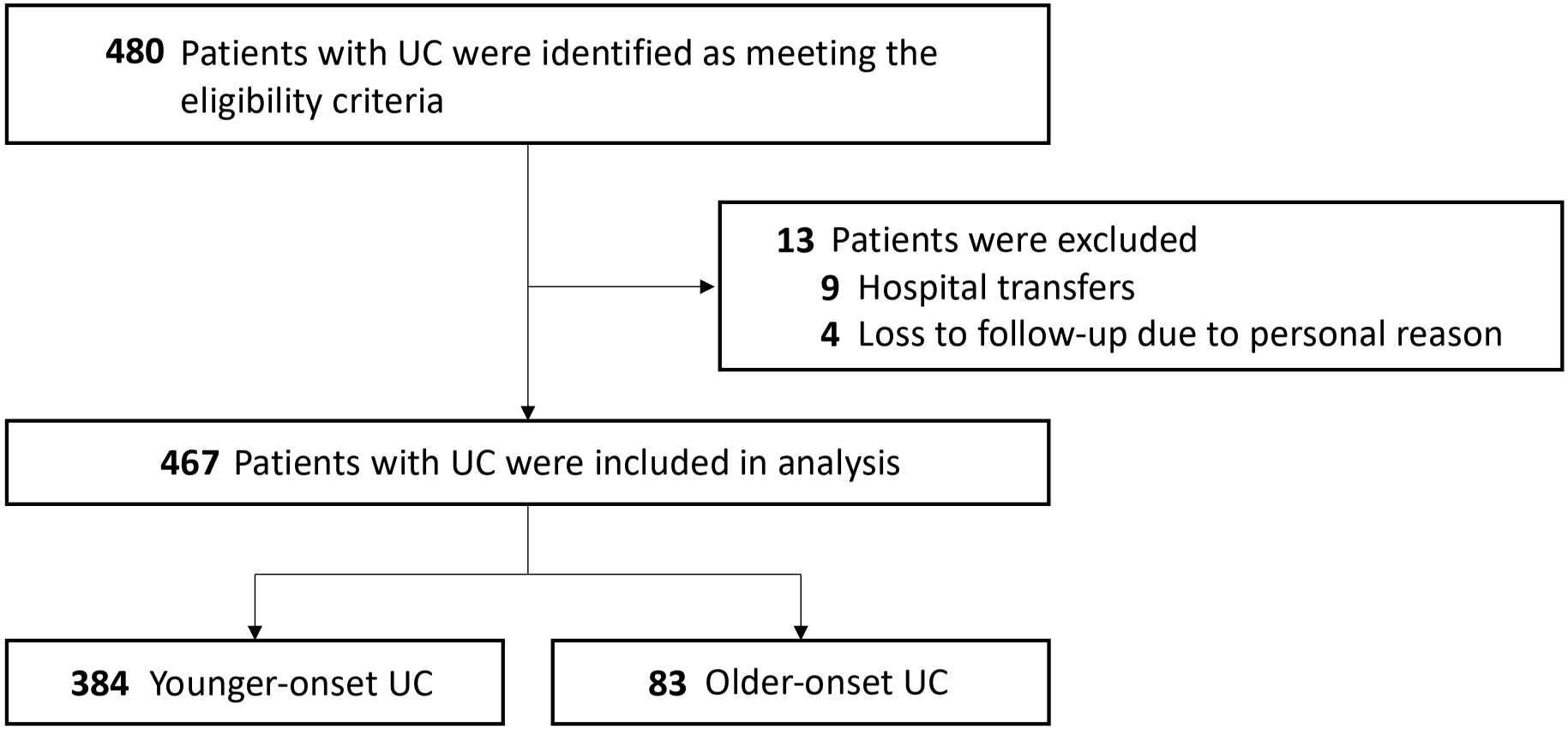
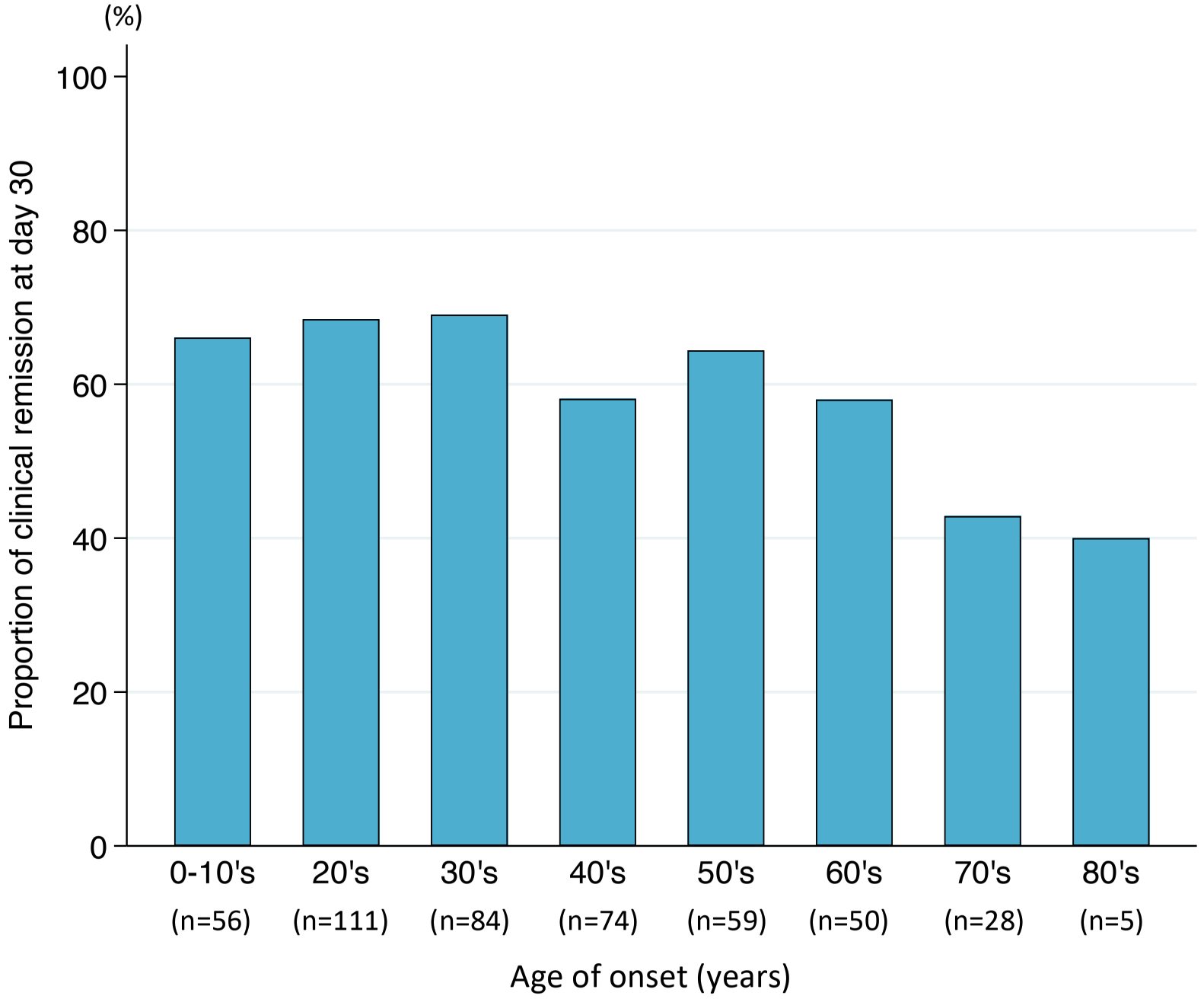
Figure 1


480 Patients with UC were identified as meeting the eligibility criteria
13 Patients were excluded
9 Hospital transfers
4 Loss to follow-up due to personal reason
467 Patients with UC were included in analysis
384 Younger-onset UC
83 Older-onset UC

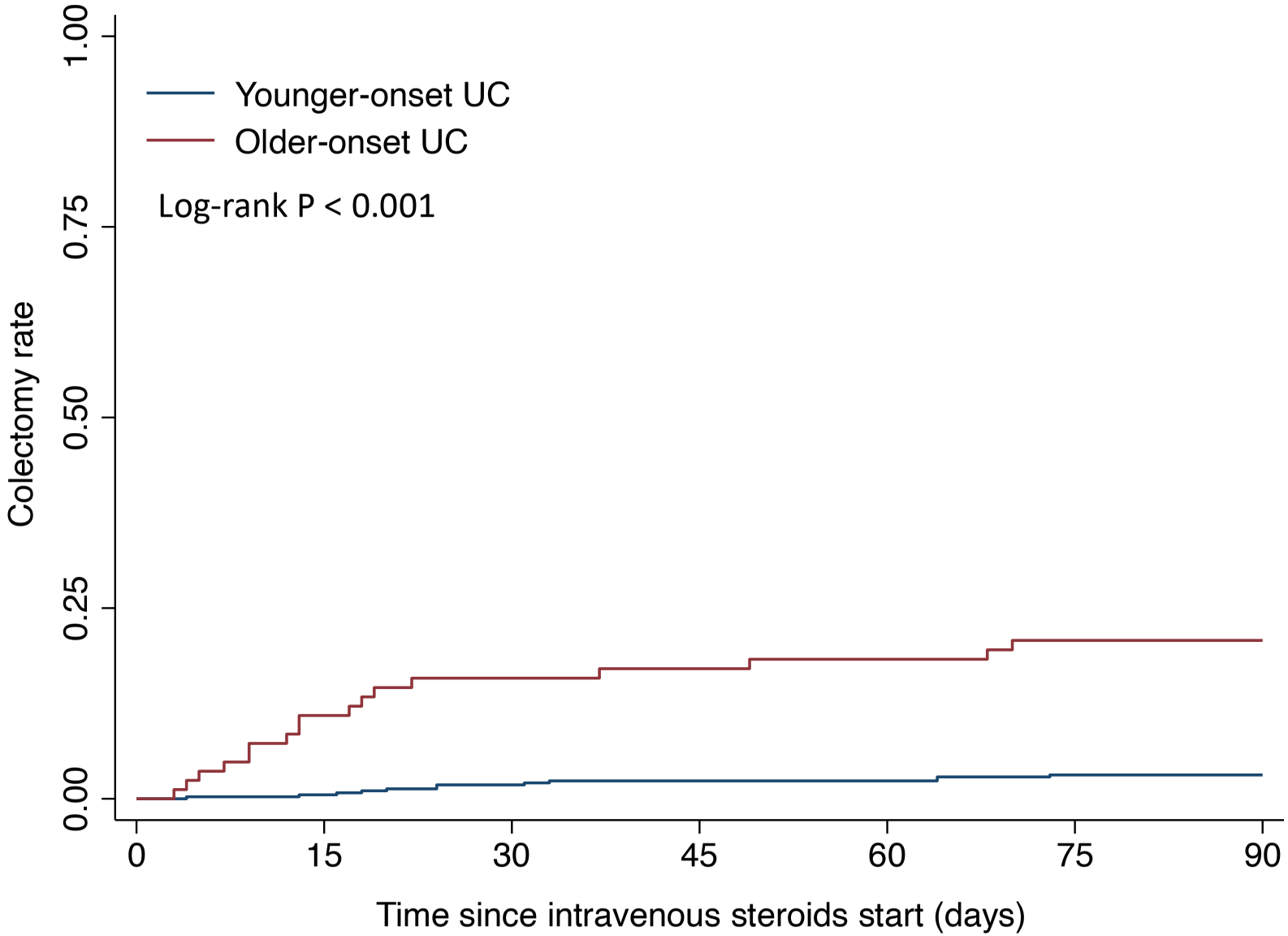
主論文

Figure 2


(%)
100
80
60
40
20
0
Proportion of clinical remission at day 30
0-10's
(n=56)
20's
(n=111)
30's
(n=84)
40's
(n=74)
50's
(n=59)
60's
(n=50)
70's
(n=28)
80's
(n=5)
Age of onset (years)

主論文

Figure 3



Number at risk

Younger-onset UC	384	382	377	375	375	372	372
Older-onset UC	83	73	68	67	66	64	63