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ORIGINAL RESEARCH ARTICLE

Factors Associated with Discontinuation of Statin Therapy in Patients with Lymphoma Aged 80 Years and Older: A Retrospective Single-Institute Study

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Abstract

Background There is little evidence to support or negate the benefits of statin therapy for primary prevention of cardiovascular disease (CVD) in lymphoma patients aged 80 years or older.

Objective We evaluated comprehensive geriatric assessment (CGA) scores and previously reported risk factors for failure of statin therapy discontinuation in lymphoma patients aged 80 years and older with the aim of identifying those in whom discontinuation of statins for primary CVD prevention is indicated.

Patients and methods Our study cohort comprised 50 patients aged 80 years and older treated with chemotherapy for lymphoma at our institute from January 2011 to July 2020. We retrospectively analyzed the associations between CGA, including Geriatric 8, instrumental activities of daily living, and Charlson comorbidity index, and previously reported factors associated with failure of statin therapy discontinuation, defined as reintroduction of statins after their discontinuation, in this patient cohort.

Results Twenty years or less of statin therapy was an independent predictor of failure of statin therapy discontinuation (hazard ratio 8.240, 95% confidence interval 1.380–49.10). There were significant differences in the rate of failure of statin discontinuation between patients receiving statins for ≥ 20 years versus < 20 years ($p = 0.010$). Multivariate analysis of CGA-related scores identified no significant risk factors for failure of statin discontinuation.

Conclusions Discontinuation of statin therapy may be indicated in lymphoma patients aged 80 years and older who have used statins for 20 years or more.

Key Points

Overall duration of statin use of 20 years or less was an independent predictor of the likelihood of failure of statin therapy discontinuation in 50 lymphoma patients aged 80 years and older who had achieved continuous chemotherapy-induced complete remission for at least 1 year.

Discontinuation of statin therapy may be indicated in lymphoma patients aged 80 years and older who have used statins for 20 years or more.

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1 Introduction

Statins are used to reduce the risk of cardiovascular disease (CVD) [1]. However, limitations in the evidence supporting statin use have been highlighted for older people without diabetes mellitus [2], especially those aged 80 years or older [3]. In particular, there is conflicting evidence for the benefit of initiating statins for primary prevention, and little evidence in patients who are frail or have multiple co-morbidities [4]. Contemporary guidance advocates an individualized approach to statin use and discontinuation among older people [5]. It has been found that neither using statins [6] nor discontinuing them [7] is associated with improved survival in patients with lymphoma; however, few data are available on interactions between statins and chemotherapy drugs for lymphoma in patients aged 80 years or older. Statin therapy should be rationalized at the time of lymphoma diagnosis, especially in patients aged 80 years and older receiving chemotherapy, because statin therapy may unnecessarily add to the therapeutic burden [7].

Comprehensive geriatric assessment (CGA) has been used to help identify older patients with lymphoma for whom standard chemotherapy is indicated [8]. Indeed, an expert panel of the American Society of Clinical Oncology suggested that clinicians should consider undertaking a CGA of older patients for whom chemotherapy is being considered [9]. However, there are few reports on CGA for lymphoma patients aged 80 years and older who are receiving attenuated doses of chemotherapy [10–12].

To fill this evidence gap in the management of older patients with lymphoma in real-world practice, we conducted a retrospective investigation at our institution. The aim of this study was to investigate CGA and previously reported factors associated with failure of statin therapy discontinuation, defined as the need for reintroduction of statins, to identify lymphoma patients aged 80 years and older for whom discontinuation of statins for primary CVD prevention is indicated.

2 Patients and Methods

2.1 Patient Selection

The inclusion criteria of this study were as follows: (1) newly diagnosed and histologically proven de novo lymphoma, including Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma according to the World Health Organization classification [13]; (2) continuous complete remission after chemotherapy for at least 1 year; (3) receiving a statin for primary prevention of CVD before diagnosis of lymphoma; (4) aged 80 years or older at the time of lymphoma diagnosis; and (5) discontinued statins following a shared decision-making process that took polypharmacy, frailty, and the potential adverse effects of chemotherapy into consideration between January 2010 and July 2020 at the Kyushu University Beppu Hospital. The exclusion criteria were as follows: (1) history of dementia (because of the difficulty in evaluating CGA); (2) history of CVD and diabetes mellitus; and (3) the treating physician's opinion that the patient had sufficient risk of active CVD to require ongoing therapy with statin medications or had other contraindications to discontinuing statin therapy.

The examined variables were as follows: age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, CGA including Geriatric 8 (G8) [14], instrumental activities of daily living (IADL) [15], and Charlson comorbidity index (CCI) [16]. Assessments of disease status included physical examination, computed tomography (CT) findings, and bone marrow analysis. Tumor responses were evaluated on positron emission tomography (PET)-CT images in accordance with the Revised Response Criteria for Malignant Lymphoma [17]. CT of the neck, thorax, abdomen, and pelvis and PET-CT were performed every 3 months for up to 24 months or until initiation of alternative chemotherapy, whichever came first. CT and PET-CT were performed by experienced radiologists at our institute.

The enrolled patients were followed every 1–3 months until death or the end of the study period. Risk factors for CVD and serum cholesterol concentrations were evaluated in all patients at least every 3 months. This retrospective observational study used data from an electronic database at our institution according to the opt-out method of our hospital website. The study was performed in accordance with institutional guidelines and the principles of the Declaration of Helsinki. The protocol was approved by our institutional review board.

2.2 End Points

The primary end point of this study was the identification of lymphoma patients aged 80 years and older in whom statin therapy could safely be discontinued by investigating CGA and risk factors known to be associated with failure of statin discontinuation. Discontinuation was defined as discontinuing statins. Failure of discontinuation was defined as reintroduction of statins in accordance with the established guidelines [18] after statin discontinuation. Secondary end points addressed two safety concerns: survival and time to first cardiovascular-related event, defined as a new cardiovascular event or an invasive cardiovascular procedure requiring hospital or emergency department admission.

2.3 Statistical Methods

We analyzed the frequencies and descriptive statistics of relevant patient variables and statin medication history in our study cohort. Continuous variables are expressed as mean and standard deviation, whereas intergroup differences in categorical variables are expressed as numbers and percentages. Patients who had not relapsed, progressed, or died were censored at the date of the last follow-up. Ninety-five percent confidence intervals (CIs) for all probabilities and *P*-values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques. To accommodate competing risks, cumulative incidence curves for failure of statin discontinuation for the two groups (duration of statin use ≥ 20 years vs. < 20 years) were estimated and the differences between them were compared using Gray's test. Competing risk events denoting failure of statin discontinuation were death and first cardiovascular-related event, defined as a new cardiovascular event or an invasive cardiovascular procedure requiring hospital or emergency department admission. For each group, logistic regression was employed to evaluate the effects of patient- and statin therapy-related variables (age < 85 years vs. ≥ 85 years; sex male vs. female; ECOG performance status 0 vs. 1; G8, ≥ 13 vs. <13; IADL ≥ 4 vs. < 4; CCI ≥ 4 vs. < 4; lymphoma-treatment-free time ≥ 2 vs. < 2 years; number of co-morbidities ≤ 5 vs. > 5; duration of statin use ≥ 20 years vs. < 20 years; and number of medications ≤ 5 vs. > 5 at the time of failure of statin discontinuation. Multivariate adjustment was performed using patient- and statin therapy-related variables potentially associated with failure of statin discontinuation. Covariates significant at $p < 0.10$ in the univariate analysis were included in the multivariate analysis. All tests were two-sided, 95% CIs were calculated, and $p < 0.05$ was considered to denote statistical significance. CGA (G8, IADL, and CCI) was assessed at the time of statin discontinuation using questionnaires supported by nurses as well as the optimal cutoff values for G8, IADL, and CCI, which were determined based on the accuracy of these variables as markers of survival according to receiver operating characteristic curves, as previously reported [19]. Analyses were conducted using Stata Version 14 (Stata Corporation, College Station, TX, USA), EZR (Saitama Medical Center, Saitama, Japan; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html) [20], which is a graphical user interface for R (R Foundation for Statistical Computing, version 2.13.0; http://www.r-project.org), and a modified version of R commander (version 1.6-3) designed to add statistical functions.

3 Results

3.1 Patients' Characteristics

Overall, 50 patients with lymphoma met the inclusion criteria. Their baseline characteristics are presented in Table 1. The mean age was 82.8 years, and 12 (24%) were aged ≥ 85 years. G8 scores were < 13 in 20/50 (40%) patients, IADL < 4 in 36/50 (72%), and CCI s > 3 in 16/50 (32%). Thirty-two patients (64%) had hypertension and were taking one or more antihypertensive medication. Twenty-six of the 50 patients (52%) had been taking statin therapy for 20 years or more. The overall rate of failure of statin discontinuation was 28%. None of the study patients developed active CVD. All patients had received mRNA coronavirus disease 2019 vaccines (BNT162b2, Pfizer/BioNTech) when they had achieved continuous complete remission after chemotherapy for at least 1 year.

3.2 Multivariate Analysis

The baseline variables identified by univariate and multivariate analyses of factors potentially influencing the failure of statin discontinuation are presented in Table 2. Independent predictors of statin discontinuation failure were statin therapy administered for 20 years or more and ≤ 154 mg/dL LDL cholesterol before statin therapy (hazard ratio 8.240, 95% CI 1.380–49.10, $p = 0.020$ and hazard ratio 0.159, 95% CI 0.032–0.774, $p = 0.022$, respectively). There were significant differences in the rate of failure of statin discontinuation between patients who had taken statins for ≥ 20 years and < 20 years ($p = 0.010$; Fig. 1). Multivariate analysis comparing CGA status, including G8, IADL, and CCI, failed to identify any significant predictors of the rate of failure of statin discontinuation in our cohort of patients with lymphoma aged 80 years and older.

4 Discussion

We compared CGA and the duration of statin therapy for primary prevention of CVD in lymphoma patients aged 80 years or older who had received chemotherapy and discontinued statin therapy based on risk assessment to minimize polypharmacy. Our main finding was that statin therapy received for ≥ 20 years at the time of discontinuation of statin therapy predicted a low failure rate of statin discontinuation 1 year after discontinuation. This finding may be useful for investigating risk reduction associated

Table 1 Characteristics of study patients

Characteristic	$n = 50$
Age (mean ± SD), years	82.8 ± 2.2
≥ 85 years old, *n* (%)	12 (24)
Sex, *n* (%)	
Male	24 (48)
Female	26 (52)
ECOG PS, *n* (%)	
0	26 (52)
1	24 (48)
G8 (mean ± SD)	12.6 ± 1.6
G8 < 13, *n* (%)	20 (40)
IADL (mean ± SD)	4.6 ± 1.3
IADL < 4, *n* (%)	36 (72)
CCI (mean ± SD)	3.3 ± 0.56
CCI > 3, *n* (%)	16 (32)
Diagnosis	
HL	4 (8)
FL	18 (36)
DLBCL	22 (44)
PTCL	6 (12)
Treatment-free time for lymphoma (mean ± SD), years	4.3 ± 3.0
< 2 years, *n* (%)	18 (36)
No. of diseases (mean ± SD)	5.5 ± 2.1
> 5, *n* (%)	18 (36)
LDL cholesterol before statin therapy (mean ± SD), mg/dL	154 ± 13.1
LDL cholesterol before discontinuing statin (mean ± SD), mg/dL	100 ± 8.6
Statin use (mean ± SD), years	17.5 ± 4.3
< 20 years, *n* (%), mean ± SD	26 (52), 13.9 ± 2.6
≥ 20 years, *n* (%), mean ± SD	24 (48), 21.5 ± 1.3
No. of medications (mean ± SD)	7.0 ± 3.1
> 5, *n* (%)	22 (44)

CCI Charlson co-morbidity index, *DLBCL* diffuse large B-cell lymphoma, *ECOG PS* Eastern Cooperative Oncology Group performance status, *FL* follicular lymphoma, *G8* Geriatric 8, *HL* Hodgkin lymphoma, *IADL* instrumental activities of daily living, *LDL* low density lipoprotein, *PTCL* peripheral T-cell lymphoma, *SD* standard deviation

with minimizing polypharmacy in lymphoma patients aged 80 years or older who have achieved complete remission.

We cannot simply compare data between prospective and retrospective studies. However, our results indicate that discontinuing statin therapy in lymphoma patients aged 80 years or older achieves a good compromise between disease control and toxicities and is thus a manageable means of reducing polypharmacy in such patients [21]. Conversely, there was no difference in the rate of failure of statin discontinuation between patients aged ≤ 85 years and those aged > 85 years. Multivariate analysis comparing CGA failed to identify any significant risk factors for the rate of failure of statin discontinuation in patients aged 80 years and older. However, the number of patients with CCI scores > 3 tended to be higher than that of patients with CCI scores ≤ 3. If further study reveals that this difference is significant, it may be attributable to the fact that nearly all patients with CCI > 3 were being treated for hypertension and many had only discontinued statin therapy for a short time.

All patients who had discontinued statin therapy were checked at our institute during the first year after statin discontinuation to ensure their safety. Although some issues such as the cost of treatment remain to be resolved, careful and intensive management, including hospitalization, likely facilitates the achievement of acceptable outcomes in extremely old patients. We suggest that discontinuing statin therapy with careful follow-up, especially during the first year after discontinuation, should be considered for patients aged 80 years or older who (i) do not have active CVD; or (ii) are not at sufficient risk of active CVD to warrant ongoing therapy with statins; and (iii) have no other contraindications to discontinuing statin therapy. These considerations

Table 2 Univariate and multivariate analyses of baseline variables potentially influencing failure of discontinuation of statins in lymphoma patients aged 80 years and older

Variable	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age < 85 years old	1.000	Reference				
≥ 85 years old	2.550	0.305–21.20	0.388			
Sex Male	1.000	Reference				
Female	1.290	0.177–9.380	0.802			
ECOG PS 0	1.000	Reference				
1	0.069	0.001–3.040	0.167			
G8 ≥ 13	1.000	Reference				
< 13	5.430	0.621–47.60	0.167			
IADL ≥ 4	1.000	Reference				
< 4	3.460	0.308–38.80	0.315			
CCI ≤ 3	1.000	Reference		1.000	Reference	
> 3	8.310	0.688–100.00	0.095	2.360	0.422–13.20	0.327
TFT ≥ 2 years	1.000	Reference				
< 2 years	0.404	0.060–2.720	0.351			
No. of diseases ≤ 5	1.000	Reference				
> 5	0.479	0.058–3.950	0.494			
LDL cholesterol before statin therapy ≤ 154 mg/dL	1.000	Reference		1.000	Reference	
> 154 mg/dL	0.192	0.047–0.773	0.020	0.159	0.032–0.774	0.022
LDL cholesterol before discontinuing statin ≤ 100 mg/dL	1.000	Reference				
> 100 mg/dL	0.939	0.234–3.780	0.930			
Statin use ≥ 20 years	1.000	Reference		1.000	Reference	
< 20 years	15.30	1.620–144.00	0.017	8.240	1.380–49.10	0.020
No. of medications ≤ 5	1.000	Reference				
> 5	3.580	0.157–81.50	0.424			

CCI Charlson comorbidity index, *CI* confidence interval, *G8* Geriatric 8, *HR* hazard ratio, *IADL* instrumental activities of daily living, *LDL* low density lipoprotein, *TFT* treatment-free time for lymphoma

[†]Univariate or multivariate competing event statistics analyzed by the logistic regression model were applied for discontinuation of statins

are important because discontinuing statins has been associated with an increased risk of active CVD [22, 23].

In this study, we found that taking statin therapy for 20 years or more was an independent predictor of successful discontinuation of statins. Checking the duration of statin therapy may guide decision-making regarding its discontinuation. Discontinuing statin therapy on this basis has potential economic implications in that it would only deliver curative-intent treatment to patients who are likely to benefit from statin medications; namely, those who are at sufficient risk of active CVD to justify ongoing statin therapy. CGA is routinely performed in inpatients as a reference [19] but not in outpatients. We excluded patients with a history of dementia, which could have skewed our evaluation of CGA. Our data may help patients better understand treatment-related risks and make informed decisions when deciding whether to continue statin therapy.

This cohort study had some other limitations, including its small sample size and single-institute nature. Objective data, such as laboratory values, and CGA data, including G8, IADL, and CCI, are reliable. However, subjective data such as non-hematological toxicity may have been underestimated because this information was dependent on medical records written by physicians before the study was planned. To maximize patient safety, we excluded patients with diabetes mellitus (DM) because randomized controlled trials have shown that statin treatment is beneficial in patients with DM [24]. To minimize bias due to disease progression, we included only patients who had achieved complete remission of their lymphomas after initial chemotherapy at a single institution and who had remained in continuous complete remission for at least 1 year after chemotherapy. We need to outline the explicit conditions to underestimate any correlations with side effects and

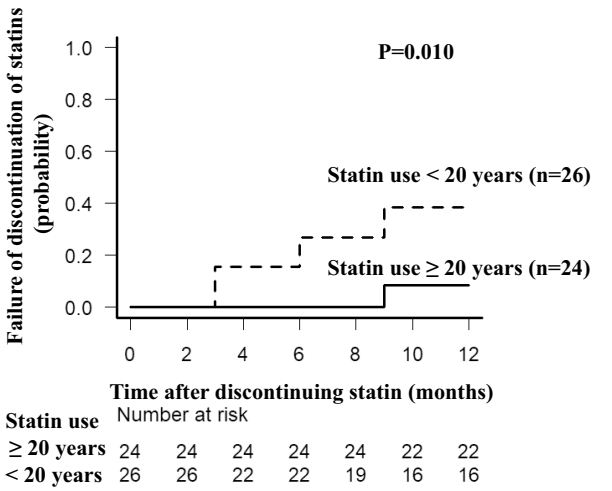

Fig. 1 Differential impact on the rate of failure of statin discontinuation according to the duration of statin therapy (< 20 vs. ≥ 20 years) in lymphoma patients aged 80 years or older

drug interactions in this study affected by selection bias. We selected this subgroup because discontinuing statin therapy in patients with a low life expectancy is relatively safe and may be associated with benefits, including improved quality of life, the use of fewer non-statin medications, and a corresponding reduction in medication costs, as previously reported [21]. Another potential limitation is that the time of diagnosis of disease progression depended on the time of performing PET-CT. Furthermore, less intensive treatment than is used in younger patients, such as R-miniCHOP [19], may have contributed to poorer treatment outcomes in our study cohort. Finally, selection bias, especially that related to the exclusion of patients with a history of dementia, and the short duration of follow-up may have skewed our analysis of patient outcomes after their initial chemotherapy.

5 Conclusion

Discontinuation of statin therapy may be indicated in lymphoma patients aged 80 years and older who have taken statins for 20 years or more. Further approaches to identify lymphoma patients aged 80 years or older who are maintaining activities of daily living after chemotherapy and in whom discontinuation of statins will likely be successful are needed.

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Declarations

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Conflict of interest Satoshi Yamasaki, Tomotake Tokunou, and Takahiko Horiuchi declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Ethics approval This study was approved by the institutional review board of Kyushu University Hospital, Japan.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material: The institutional review board of Kyushu University Hospital, Japan, does not allow open access. However, on reasonable request, additional analyses can be performed after contacting the corresponding author.

Code availability Not applicable.

Authors' contributions Satoshi Yamasaki designed the study, analyzed the data, and prepared the manuscript. Satoshi Yamasaki, Tomotake Tokunou, and Takahiko Horiuchi prepared and reviewed the manuscript. All authors met the International Committee of Medical Journal Editors criteria for authorship of this article, take responsibility for the integrity of the work as a whole, and have read and approved the final manuscript.

References

1. Cai T, Abel L, Langford O, Monaghan G, Aronson JK, Stevens RJ, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ. 2021;374:n1537.
2. Awad K, Mohammed M, Zaki MM, Abushouk AI, Lip GYH, Blaha MJ, et al. Association of statin use in older people primary prevention group with risk of cardiovascular events and mortality: a systematic review and meta-analysis of observational studies. BMC Med. 2021;19:139.

3. Gulliford M, Ravindrarajah R, Hamada S, Jackson S, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study. Age Ageing. 2017;46:1001–5.
4. Luotola K, Jyväkorpi S, Urtamo A, Pitkälä KH, Kivimäki M, Strandberg TE. Statin treatment, phenotypic frailty and mortality among community-dwelling octogenarian men: the HBS cohort. Age Ageing. 2020;49:258–63.
5. Rasmussen P, Yandrapalli S, Aronow W. Statin therapy for primary cardiovascular prevention in adults older than 75 years. Kardiol Pol. 2021;79:18–24.
6. Ye X, Mneina A, Johnston JB, Mahmud SM. Associations between statin use and non-Hodgkin lymphoma (NHL) risk and survival: a meta-analysis. Hematol Oncol. 2017;35:206–14.
7. Stavrou EP, Buckley N, Olivier J, Pearson SA. Discontinuation of statin therapy in older people: does a cancer diagnosis make a difference? An observational cohort study using data linkage. BMJ Open. 2012;2: e000880.
8. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115:4547–53.
9. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36:2326–47.
10. Carson KR, Riedell P, Lynch R, Nabhan C, Wildes TM, Liu W, et al. Comparative effectiveness of anthracycline-containing chemotherapy in United States veterans age 80 and older with diffuse large B-cell lymphoma. J Geriatr Oncol. 2015;6:211–8.
11. Bai JF, Han HX, Feng R, Li JT, Wang T, Zhang CL, Liu H. Comprehensive geriatric assessment (CGA): a simple tool for guiding the treatment of older adults with diffuse large B-cell lymphoma in China. Oncologist. 2020;25:e1202-1208.
12. Lee S, Fujita K, Negoro E, Morishita T, Oiwa K, Tsukasaki H, et al. Impact of relative dose intensity of standard regimens on survival in elderly patients aged 80 years and older with diffuse large B-cell lymphoma. Haematologica. 2020;105:e415–8.
13. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
14. Martinez-Tapia C, Paillaud E, Liuu E, Tournigand C, Ibrahim R, Fossey-Diaz V, et al. Prognostic value of the G8 and modified-G8 screening tools for multidimensional health problems in older patients with cancer. Eur J Cancer. 2017;83:211–9.
15. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86.
16. 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.
17. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86.
18. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082–143.
19. Yamasaki S, Matsushima T, Minami M, Kadowaki M, Takase K, Iwasaki H. Clinical impact of comprehensive geriatric assessment in patients aged 80 years and older with diffuse large B-cell lymphoma receiving rituximab-mini-CHOP: A single-institute retrospective study. Euro Geriatric Med. 2022;13:195–201.
20. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
21. Kutner JS, Blatchford PJ, Taylor DH Jr, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015;175:691–700.
22. Scheen AJ. Statins and clinical outcomes with COVID-19: meta-analyses of observational studies. Diabetes Metab. 2020;47: 101220.
23. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. Lancet. 2020;396:1644–52.
24. Rea F, Biffi A, Ronco R, Franchi M, Cammarota S, Citarella A, et al. Cardiovascular outcomes and mortality associated with discontinuing statins in older patients receiving polypharmacy. JAMA Netw Open. 2021;4: e2113186.