 DOI: https://doi.org/10.5114/ceji/209783

Improved outcomes in relapsed and refractory multiple myeloma: a single-center real-world analysis of evolving treatment standards

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Abstract

Novel drugs have recently been introduced into the treatment of relapsed and refractory multiple myeloma (RRMM). Their impact on clinical outcomes in real-world settings remains to be clarified. To address this question, we evaluated survival outcomes in two real-world RRMM patient cohorts at our center, stratified by the time point when anti-CD38 monoclonal antibody treatment became available in routine clinical practice (January 1, 2013-June 30, 2018 vs. July 1, 2018-December 31, 2022). Patients in the post-July 2018 cohort had superior outcomes, with improved progression-free survival (PFS) and overall survival (OS) at 2-6 lines of therapy (LOT). This was statistically significant at 2-6 LOT for PFS and 2-4 LOT for OS ($p < 0.05$). Among triple-class exposed patients (previous or ongoing exposure to proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies), OS was significantly superior at 2-4 LOT and PFS superior at 4 LOT. Thus, this study provides evidence that the evolving standard-of-care in RRMM in recent years has markedly improved clinical outcomes. Our results emphasize the importance of using modern treatment options in the RRMM setting and the continued need to develop novel treatments to further improve patient outcomes.

Key words: *monoclonal antibody, treatment outcomes, multiple myeloma, real-world, relapsed/refractory, treatment sequence.*

(Cent Eur J Immunol 2026; 51: 1-11)

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy, characterized by recurrent relapses and therapeutic resistance. Despite the use of several novel drugs in the last two decades, MM remains incurable [1]. The introduction of these treatments into the standard-of-care (SOC) has been effective in controlling the disease and even producing long-lasting remissions [2, 3]. Nevertheless, relapse and progression invariably occur [3, 4]. Throughout the course of the disease, most surviving patients will eventually develop relapsed or refractory MM (RRMM) with prior exposure or even resistance to all available treatments [5-7]. Studies indicate that refractoriness to treatments increases with each relapse, which is associated with the accumulation of mutations and genetic alterations [7, 8].

Several immunotherapeutic drugs, including anti-CD38 monoclonal antibodies (mAb) and bispecific antibodies with a T-cell engager domain, have been integrated into clinical practice for RRMM. Studies demonstrate improved patient outcomes such as extended survival [9, 10]. Anti-CD38 mAb induce antibody-dependent cellular toxicity and phagocytosis, alongside other immunomodulatory effects. Bispecific antibodies with a T-cell engager domain, which binds a tumor-specific antigen, and CD3, which activates T cells, represent another promising class of drugs [11, 12]. These novel treatments are important

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Submitted: 11.03.2025, Accepted: 21.08.2025

additions to the treatment options in RRMM and require the development of updated treatment guidelines [13, 14]. Moreover, there is a shortage of studies assessing the efficacy of these novel drugs in the context of the current SOC in RRMM, as well as a lack of consensus regarding optimal treatment combinations and the timing of their utilization [6]. While current guidelines provide several alternatives, none are definitive, nor is granularity purveyed at the local level to aid clinicians in streamlining treatment regimens. Real-world evidence studies may assist in generating clinical evidence in the RRMM setting [15].

This study aimed to evaluate the current treatment landscape in RRMM and the influence of the evolving SOC on patient outcomes. For this purpose, we assessed progression-free survival (PFS) and overall survival (OS) in two real-world RRMM patient cohorts at our center, which were separated by the date when anti-CD38 mAb became available in routine clinical practice. Moreover, we studied the impact of exposure to three SOC drug classes with different mechanisms of action – proteasome inhibitors (PI), immunomodulatory drugs (IMiD), and anti-CD38 mAb – on survival outcomes. To test this, we analyzed whether patients exposed to all three drugs exhibited superior outcomes compared to those who were not.

Material and methods

Patients

This retrospective, observational study was conducted at a single tertiary hematology center in Sweden, using pseudonymized clinical data from patients diagnosed with RRMM between 2013 and 2022. Patients ≥ 18 years at the time of MM diagnosis, with RRMM according to the International Myeloma Working Group (IMWG) criteria [16], and treated with ≥ 1 subsequent line of therapy (LOT) following first-line treatment were included. The definition of a LOT and the number of therapies were determined according to Rajkumar *et al*. [17].

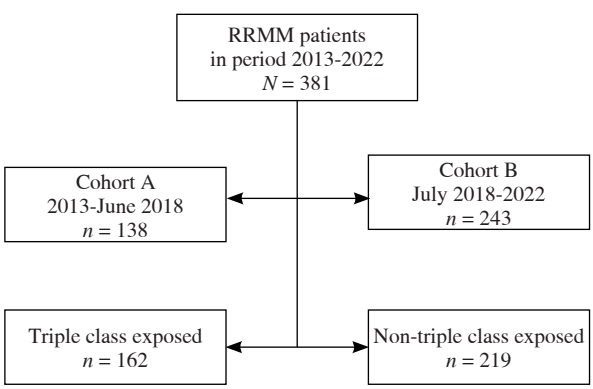

Fig. 1. Selection process for patient cohorts in the study. Cohorts A and B were stratified according to date of most recent relapsed and refractory multiple myeloma (RRMM) event, with the cut-off date when anti-CD38 mAb became available at our center: cohort A 2013-June 30, 2018 and cohort B July 1, 2018-2022. For the separate analysis of patients triple-class exposed vs. non-triple-classed exposed, stratification was based on the entire cohort, due to the limited number of patients in cohort A (n = 14)

The study population was stratified by the date of their most recent RRMM event into two cohorts: cohort A – the most recent relapse between January 1, 2013 and June 30, 2018; and cohort B – the most recent relapse between July 1, 2018 and December 31, 2022. The two cohorts were separated by the introduction of anti-CD38 mAb to the treatment of MM at our center. Patients with an RRMM event before June 30, 2018, who started a LOT that continued into the time period of cohort B were retained in cohort A. The patient selection process is depicted in Figure 1.

Survival outcomes

Primary endpoints were PFS, defined as the time from LOT initiation to disease progression or death, and OS, defined as the time from LOT initiation to death of any cause. Patients were censored at the date of their last follow-up if no event had occurred. If a subsequent LOT was started without prior disease progression (for example due to adverse effects), patients were censored at the date of initiation of the subsequent LOT for the calculation of PFS. Outcomes were evaluated from the start of the second LOT (2L) and for each subsequent LOT in both cohorts. Our study design followed patients' treatment regimens for each LOT from the first relapse (2L) onwards, until death or the date of the last follow-up. This was performed even if 2L was administered before the cut-off date (July 1, 2018) for stratification to cohort B with regards to the latest RRMM event, in order to yield comparative data across all LOT in both groups.

Additionally, we performed a separate analysis of survival outcomes at each LOT for all those who were triple-class exposed (TCE) at the time of study inclusion. We defined TCE as having received at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb at any time point of the disease, including both previous and ongoing treatments. The outcomes were compared with patients not exposed to all three drug classes (non-TCE) among all patients. We did not perform an assessment on triple-class refractory RRMM patients due to the limited number of subjects at our center during the study period (n = 21 across all LOT).

Statistical analysis

No formal power analysis was conducted for this study, due to our retrospective study design and inclusion of all RRMM patients with available data at our center. Descriptive data parameters were calculated as mean, standard de-

viation, median, range, and interquartile range, depending on the variable. Missing data were handled by censoring in time-to-event analyses and reporting as percentages in descriptive statistics. For numerical variables, the comparative analyses were conducted with the Mann-Whitney *U*-test, while for categorical variables, the chi-squared test was used. The Kaplan-Meier method was used to calculate survival outcomes, and log-rank tests were employed to assess statistical significance. A p-value < 0.05 was interpreted as statistically significant. A multivariate Cox proportional hazard model was employed to explore potential confounders for PFS and OS at 2L, including age ≥ 65 years at MM diagnosis, gender, International Staging System (ISS) stage (using stage I as the reference), cytogenetic risk profile at MM diagnosis, stratification to cohort A or B, anti-CD38 mAb exposure, and triple-class exposure. Missing values for ISS and cytogenetic risk led to the exclusion of those patients from univariable analysis. For all other variables, complete data were used for univariable analysis without any exclusion. Variables with a p-value < 0.05 in the univariate analysis were included in the multivariable model. If both anti-CD38 mAb exposure and triple-class exposure were significant in the univariable analysis, only anti-CD38 mAb exposure was used in the multivariable analysis. To ensure consistency, the multivariable model excluded patients with missing ISS or cytogenetic risk profile data.

Descriptive analysis was performed in Microsoft Excel (version 2408, Microsoft) and IBM SPSS Statistics (version 29.0.1, IBM). Time-to-event analyses and Cox regression analyses were performed in R (version 4.4.1, R Foundation for Statistical Computing).

Ethical considerations

This study was approved by the Swedish Ethical Review Authority (ethical permit 2014/526-31/3 and 2019-04973) and was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

Results

We assessed the impact of the current SOC on clinical outcomes in a real-world cohort of RRMM patients compared to a previous RRMM cohort with relapse or progression during the preceding 5.5 years, and observed that both PFS and OS were significantly improved at 2-6L for PFS and 2-4L for OS. Additionally, we found superior OS at 2-4L for TCE patients compared to non-TCE patients.

We identified a total of 381 RRMM patients according to the study criteria, 138 in cohort A and 243 in cohort B. Clinical characteristics for both cohorts are summarized in Table 1. Overall, the median age at MM diagnosis was 69 years, 57% were male, and the proportions of ISS disease stage I, II, and III were 15%, 46%, and 23%, respectively, while 17% were indeterminable due to missing data. Furthermore, 188 patients (49%) had an available cytogenetic risk profile at MM diagnosis. Of these, 70 subjects (37% of available) had high-risk disease, defined as the presence of the chromosomal aberrations del(17p), t(4;14), t(14;16) and/or amp/gain1q. The median duration of follow-up from MM diagnosis to death or the date of last visit was 44.3 months (IQR: 24.3-71.0) for cohort A and 63.3 (IQR: 35.3-90.8) months for cohort B. During follow-up, cohort A had a median of 3L (range 2-9) and cohort B 2L (range 2-7). Analysis of survival outcomes were conducted for 2-6L, as the sample size at 7L and beyond was insufficient to provide meaningful results.

The univariate analysis exploring possible confounding patient characteristics at the start of 2L, with missing data points removed, showed that the following parameters were associated with inferior PFS: age ≥ 65 years at MM diagnosis (HR = 2.03, 95% CI: 1.55-2.66, $p < 0.001$), ISS stage III (HR = 1.50, 95% CI: 1.02-2.19, $p = 0.040$) and high-risk cytogenetics (HR = 1.70, 95% CI: 1.22-2.36, $p = 0.002$). Stratification to cohort B was associated with superior PFS (HR = 0.68, 95% CI: 0.54-0.85, $p = 0.001$). Upon including these parameters in a multivariate analysis, age ≥ 65 years at MM diagnosis (HR = 1.53, 95% CI: 1.04-2.24, $p = 0.030$) and high-risk cytogenetics (HR = 1.70, 95% CI: 1.20-2.41, $p = 0.003$) were still significant, while ISS III and stratification to cohort B were not. Factors at 2L that were associated with inferior OS in univariate analysis were: age ≥ 65 years at MM diagnosis (HR = 2.47, 95% CI: 1.74-3.52, $p < 0.001$), ISS stage III (HR = 2.06, 95% CI: 1.29-3.28, $p = 0.003$), and high-risk cytogenetics (HR = 1.98, 95% CI: 1.32-2.96, $p = 0.001$). Factors associated with superior OS were: stratification to cohort B (HR = 0.42, 95% CI: 0.32-0.55, $p < 0.001$), anti-CD38 mAb exposure (HR = 0.52, 95% CI: 0.39-0.70, $p < 0.001$) and triple-class exposure (HR = 0.54, 95% CI: 0.40-0.72, $p < 0.001$). Upon including these parameters in a multivariate analysis, age ≥ 65 years at MM diagnosis (HR = 1.95, 95% CI: 1.17-3.26, $p = 0.011$) and high-risk cytogenetics (HR = 2.13, 95% CI: 1.35-3.38, $p = 0.001$) remained significant.

By examination of outcomes, we determined that cohort B exhibited significantly superior PFS than cohort A at 2-6L. Median PFS at 2L was 15.5 vs 7.8 months (HR = 0.68, 95% CI: 0.54-0.85, $p < 0.001$), at 3L 11.9 vs. 4.4 months (HR = 0.50, 95% CI: 0.38-0.66, $p < 0.001$), at 4L 10.1 vs. 2.3 months (HR = 0.46, 95% CI: 0.30-0.69, $p < 0.001$), at 5L 8.0 vs. 2.8 months (HR = 0.47, 95% CI: 0.22-1.00, $p = 0.045$), and at 6L 10.0 vs. 1.6 months (HR = 0.27, 95% CI: 0.10-0.76, $p = 0.008$). Median PFS at 2-6L is shown in Figure 2A. Similarly, significantly superior OS was observed in cohort B compared to cohort A at 2-4L. Median OS at 2L was 69.2 vs. 22.2 months (HR = 0.42, 95% CI: 0.32-0.55, $p < 0.0001$), at 3L 42.8 vs. 9.4 months (HR = 0.41, 95% CI: 0.30-0.56, $p < 0.0001$), and at 4L 19.9 vs. 6.7 months (HR = 0.52, 95% CI: 0.34-0.81,

Table 1. Patient characteristics of cohorts A and B

Characteristic	Cohort A (n = 138)	Cohort B (n = 243)	P-value
Age at MM diagnosis (years), median (range)	71 (26-93)	69 (32-92)	0.039
Gender (male), *n* (%)	73 (53)	146 (60)	0.173
ISS at MM diagnosis (categorical), *n* (%)			
I	17 (12)	39 (16)	0.338
II	65 (47)	110 (45)	
III	37 (27)	50 (21)	
Unknown	19 (14)	44 (18)	
Cytogenetic profile at MM diagnosis (categorical), *n* (%)			
High-risk†	30 (22)	40 (16)	0.066
Standard	35 (25)	83 (34)	
Unknown	73 (53)	120 (49)	
Patients starting each LOT (categorical), *n* (%)			
2	138 (100)	243 (100)	0.007
3	97 (75)	158 (65)	
4	52 (38)	76 (31)	
5	24 (17)	14 (6)	
6	16 (12)	9 (4)	
≥ 7	8 (6)	1 (< 1)	
Autologous stem cell transplant at front-line, *n* (%)	39 (28)	89 (37)	0.097
Exposure to PI, IMiD and anti-CD38 mAb during all LOT‡, *n* (%)	14 (10)	148 (61)	< 0.001

Cohort A: Most recent RRMM event between 2013 and June 2018. Cohort B: Most recent RRMM event between July 2018 and 2022. Chi-squared test (categorical variables) and Mann-Whitney U-test (numerical variables) were used to compare cohorts. †Defined as presence of t(4;14), t(14;16), del17p or amp/gain1q. ‡Includes ongoing LOT. MM – multiple myeloma, ISS – International Staging System, PI – proteasome inhibitor, IMiD – immunomodulatory drug, mAb – monoclonal antibody, LOT – line of therapy

p = 0.0029). Median OS at 5L was 18.4 vs. 8.0 months (HR = 0.55, 95% CI: 0.25-1.19, p = 0.12) and at 6L 10.0 vs. 3.3 months (HR = 0.46, 95% CI: 0.17-1.28, p = 0.13). Median OS at 2-6L is shown in Figure 2B.

The clinical characteristics of TCE and non-TCE patients are summarized in Table 2. In our separate analysis of outcomes in patients with prior or ongoing TCE across all LOT, we observed significantly longer PFS at 4L, with TCE vs non-TCE having a median PFS of 10.5 vs. 3.7 months (HR = 0.49, 95% CI: 0.33-0.75, p < 0.001), respectively. However, while the trend was towards superior PFS in TCE vs non-TCE patients at all other LOT, the differences were not statistically significant. Median PFS for TCE vs non-TCE patients at 2-6L is shown in Figure 3A. In contrast, median OS was superior in TCE patients at 2-4L compared to non-TCE patients. Median OS at the start of 2L was 68.4 vs. 29.4 months (HR = 0.54, 95% CI: 0.40-0.72, p < 0.001), 3L 34.7 vs. 13.8 months (HR = 0.54, 95% CI: 0.39-0.74, p < 0.001), and 4L 19.9 vs. 6.7 months (HR = 0.48, 95% CI: 0.31-0.75, p < 0.001). Median OS for TCE vs. non-TCE patients at 2-6L is shown in Figure 3B.

Discussion

This study provided evidence that the evolving SOC in RRMM in recent years has markedly improved patient outcomes. Our analysis of a real-world patient cohort with the most recent disease progression or relapse between June 2018 and December 2022 revealed longer PFS and OS than RRMM patients with relapses during the previous 5.5 years during early LOT (Fig. 2A, B). The difference was statistically significant at 2-6L for PFS and 2-4L for OS. This indicates that the introduction and implementation of new drugs and treatment combinations at our center have positively influenced patient outcomes.

Furthermore, we observed superior OS in patients with previous or ongoing TCE (PI, IMiD and anti-CD38 mAb exposure) at their most recent RRMM event, compared to patients not exposed to all three drugs during follow-up (Figure 3B). In part, this can be attributed to the addition of anti-CD38 mAb in the treatment arsenal, and this finding supports our hypothesis that the use of multiple drugs with different mechanisms of action allows for superior disease control, which ultimately improves patient out-

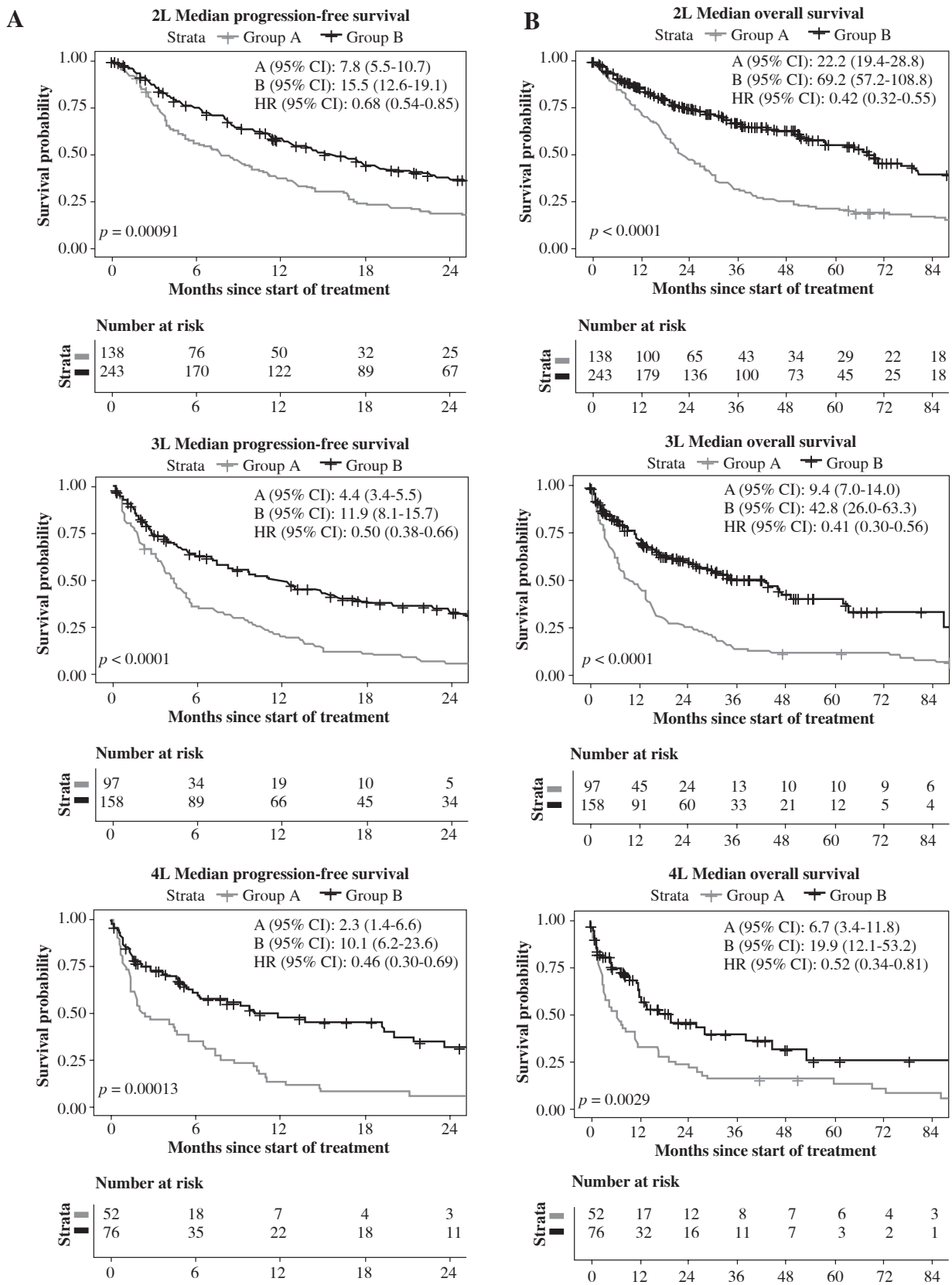

Fig. 2. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) at 2-6L. RRMM patients with last relapse between 2013 and 2018 June in grey (cohort A). Relapsed and refractory multiple myeloma (RRMM) patients with last relapse between 2018 July and 2022 in black (cohort B). Cohort B exhibited significantly ($p < 0.05$) superior median PFS at 2-6 lines of therapy (L), and significantly superior median OS at 2-4L

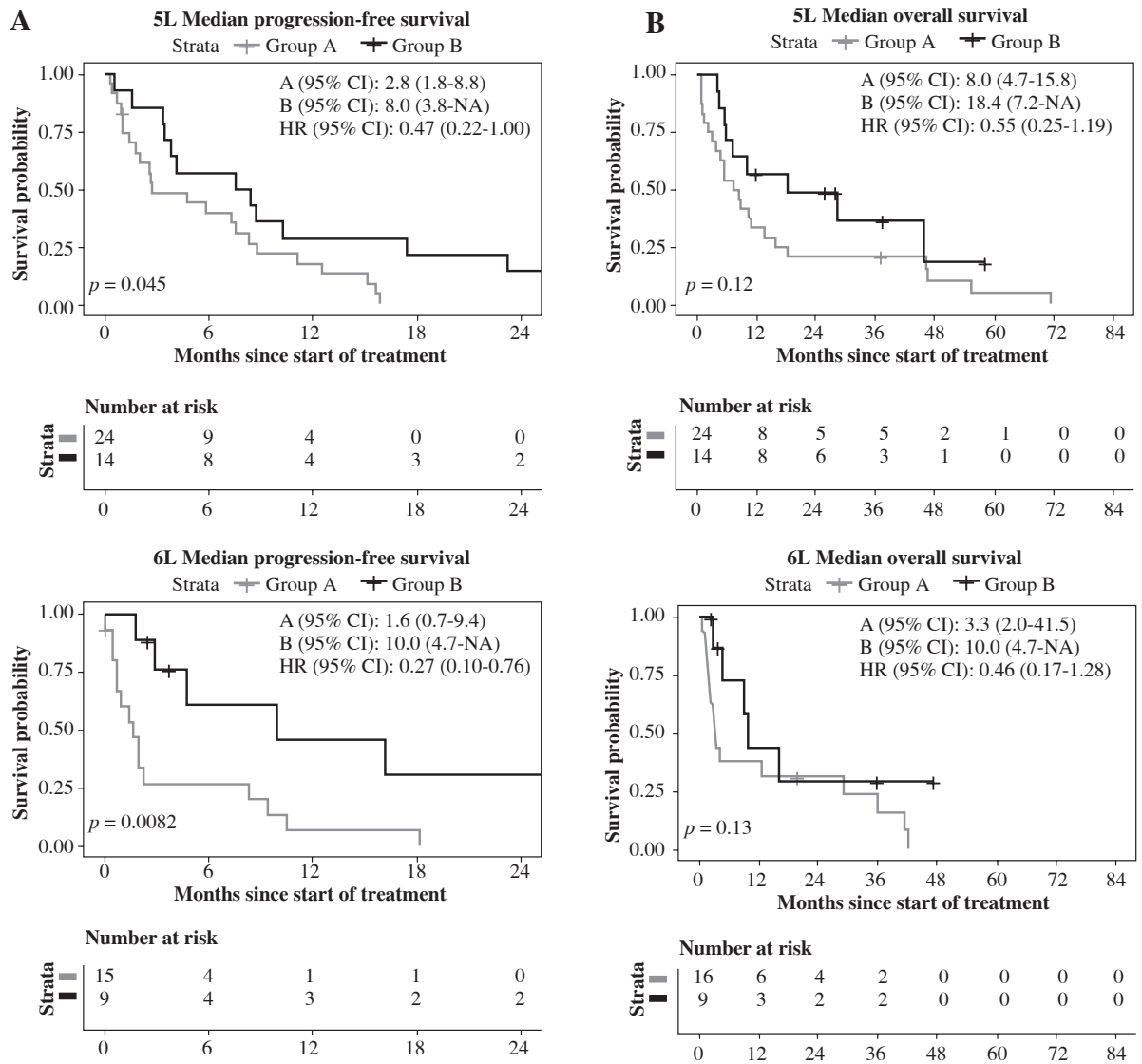

Fig. 2. Cont. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) at 2-6L. RRMM patients with last relapse between 2013 and 2018 June in grey (cohort A). Relapsed and refractory multiple myeloma (RRMM) patients with last relapse between 2018 July and 2022 in black (cohort B). Cohort B exhibited significantly ($p < 0.05$) superior median PFS at 2-6 lines of therapy (L), and significantly superior median OS at 2-4L

comes. However, while a trend towards improved PFS in TCE patients was suggested in our analysis, the differences across all LOT were not statistically significant aside from 4L (Fig. 3A).

The observed difference in administered LOT in cohorts A and B (median 3L vs. 2L) likely reflects the shorter PFS and inferior treatment responses in the earlier cohort, necessitating additional LOT. Furthermore, since our study included patients based on the most recent RRMM event, patients in cohort A are more likely to have received chemotherapy-based regimens in early LOT before pharmaceutical classes such as PI and IMiD were commonly administered at front-line therapy and early lines of RRMM treatment. In contrast, patients in cohort B are more likely to have been treated with these newer drugs. These findings underscore the importance of optimizing early LOT with modern regimens to delay disease progression. In our multivariate analysis of possible confounding factors, we discovered that age ≥ 65 and high-risk cytogenetics were the most important parameters impacting outcome at the start of 2L. However, in our patient population, cytogenetic profile was frequently missing, which may have influenced outcomes in the Cox regression model. Furthermore, ISS stage III and allocation to cohort B were significant

Table 2. Characteristics of patients with previous or ongoing triple-class exposure (TCE) compared to patients not triple-class exposed (non-TCE)

Characteristic	TCE (n = 162)	Non-TCE (n = 219)	P-value
Age at MM diagnosis (years), median (range)	68 (32-87)	72 (26-93)	< 0.001
Gender (male), *n* (%)	92 (57)	127 (58)	0.815
ISS at MM diagnosis (categorical), *n* (%)			
I	29 (18)	27 (12)	0.464
II	73 (45)	102 (47)	
III	36 (22)	151 (23)	
Unknown	24 (15)	39 (18)	
Cytogenetic profile at MM diagnosis (categorical), *n* (%)			
High-risk†	38 (23)	32 (15)	0.033
Standard	53 (33)	65 (30)	
Unknown	71 (44)	122 (56)	
Patients starting each LOT (categorical), *n* (%)			
2	162 (100)	219 (100)	< 0.001
3	127 (78)	128 (58)	
4	68 (42)	60 (27)	
5	17 (10)	21 (10)	
6	11 (7)	14 (6)	
≥ 7	2 (1)	7 (3)	
Autologous stem cell transplant at front-line, *n* (%)	66 (41)	62 (28)	0.011

TCE – previous or ongoing treatment with proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies across all LOT. Non-TCE – patients not treated with proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies across all LOT. Chi-squared test (categorical variables) and Mann-Whitney U-test (numerical variables) were used to compare cohorts. †Defined as presence of t(4;14), t(14;16), del17p or amp/gain1q. MM – multiple myeloma, ISS – International Staging System, LOT – line of therapy

predictors of PFS and OS in the univariate analysis, but lost significance in our multivariate model. This may be due to collinearity between variables, such as age and ISS or between anti-CD38 mAb exposure and assignment to cohort B.

Our results align with a study which reported outcomes of newly diagnosed MM patients between 2008 and 2015 using the Swedish Myeloma Registry [18]. The authors reported significantly improved relative survival in patients with MM diagnosed at the end of the study period. Additionally, our findings are consistent with previous real-world studies exploring RRMM outcomes using real-world data, which indicate superior outcomes in modern RRMM cohorts. For instance, a U.S. study analyzed RRMM treatment outcomes from 2011 to May 2017 within the International Oncology Network, and found that patients (n = 456) receiving newer treatment options (defined as pomalidomide, carfilzomib, elotuzumab, panobinostat, daratumumab, ixazomib and bortezomib-lenalidomide combination) had superior survival compared to older RRMM treatment regimens [19]. The authors reported numerically higher median PFS at 2-5L, 7.5 vs. 6.8 months, 4.9 vs. 4.8 months, 2.9 vs. 3.4 months, and 4.6 vs. 1.5 months, respectively, when comparing new and older treatments. Similarly, median OS at 2-5L was 28.1 vs. 21.3 months, 15.4 vs. 10.9 months, 8.7 vs. 5.1 months, and 6.3 vs. 3.4 months, respectively. An Italian single-center study which followed 413 patients between 2011 and 2021 from MM diagnosis, where 200 patients started 2L, reported a median OS of 38.3, 24.0, 12.2, and 10.5 months at 2-5L. Median PFS at 2-5L was 19.5, 10.3, 6.0, and 4.7 months, respectively [20]. In contrast, a Spanish study comparing RRMM patients at 2-3L treated with and without anti-CD38 mAb reported a relatively modest superior median PFS in the anti-CD38 treated group (22.4 vs. 20.9 months) [21]. The study enrolled patients from 52 hospitals, and encompassed 171 RRMM patients at first or second relapse between October 2017 and October 2019. However, the duration of follow-up in this study was relatively short and median OS was not reached at the time of the report.

Our study is associated with some limitations. As this study was based on a real-world data source (clinical records), missing data points may have influenced

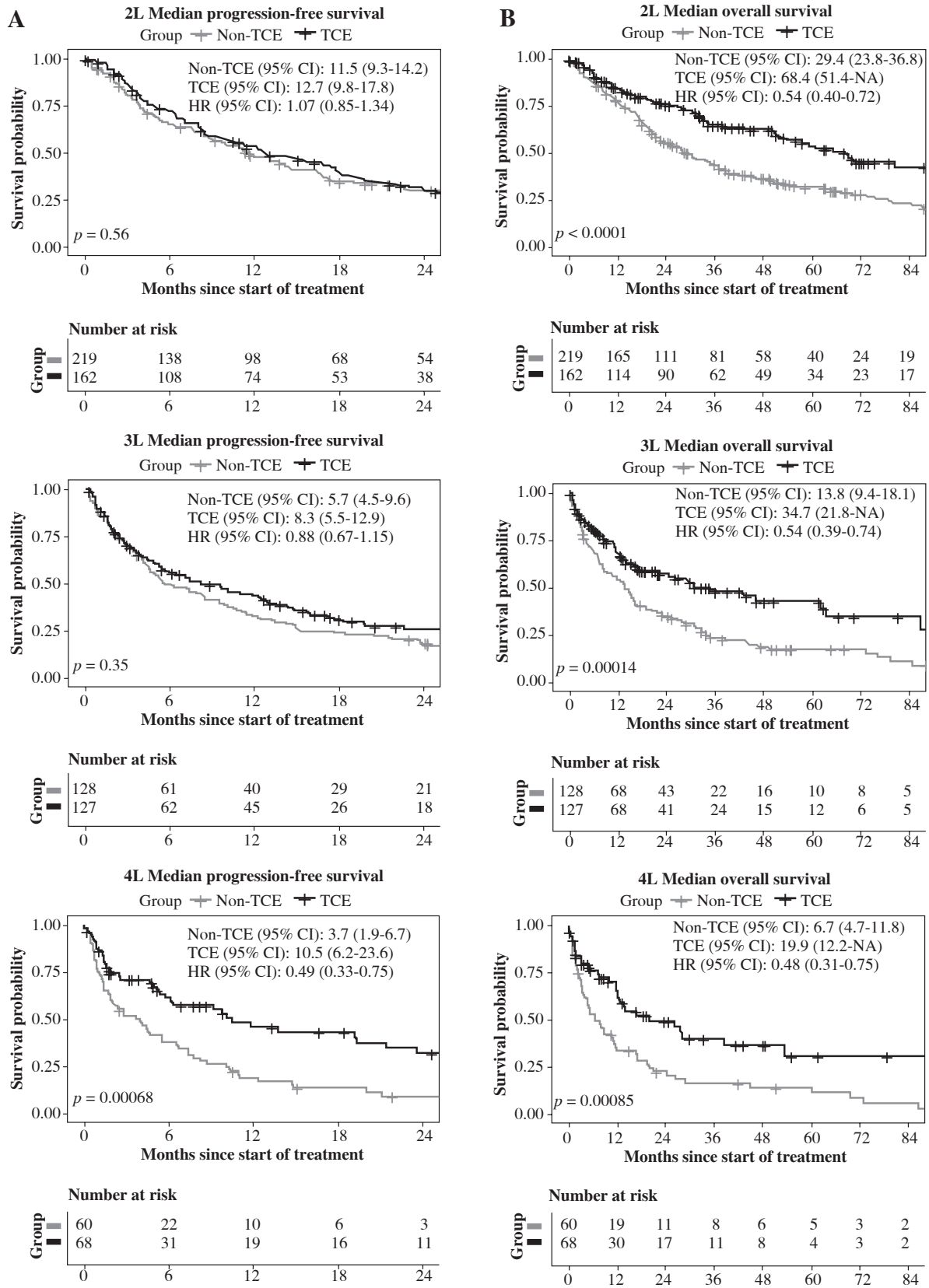

Fig. 3. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) at 2-6L in triple-class exposed (TCE) patients (black) vs. patients not exposed (grey). TCE was defined as exposure to PI, IMiD and anti-CD38 mAb across all LOT, including previous, ongoing as well as exposure in future LOT during follow-up. TCE patients exhibited significantly ($p < 0.05$) superior median PFS at fourth line of therapy (L), and superior median OS at 2-4L

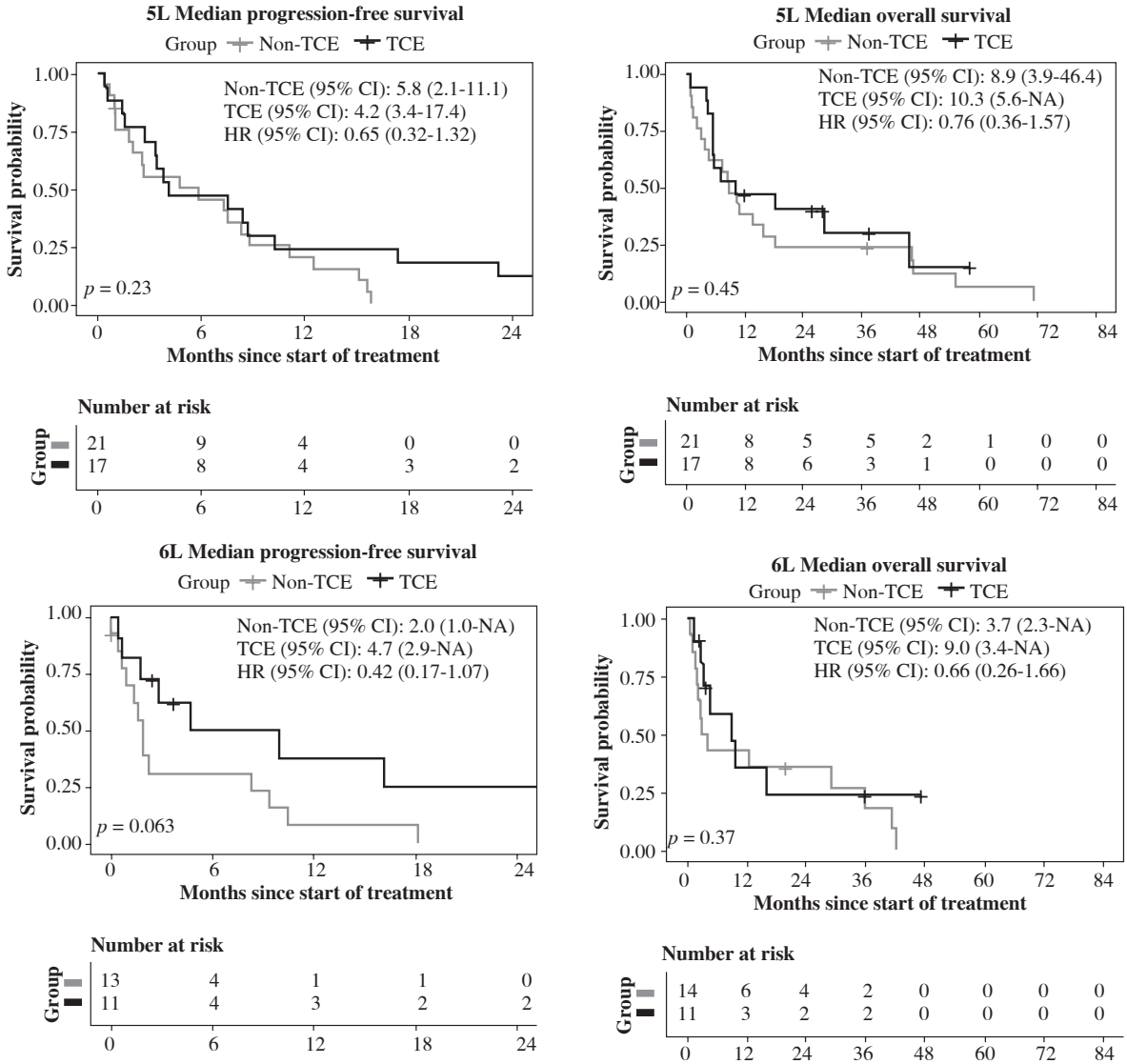

Fig. 3. Cont. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) at 2-6L in triple-class exposed (TCE) patients (black) vs. patients not exposed (grey). TCE was defined as exposure to PI, IMiD and anti-CD38 mAb across all LOT, including previous, ongoing as well as exposure in future LOT during follow-up. TCE patients exhibited significantly ($p < 0.05$) superior median PFS at fourth line of therapy (L), and superior median OS at 2-4L

the results. External validation and generalizability may be impacted by the single-center study design. While our center is among the largest hematology units in the Nordic countries, the limited cohort size at a mainly metropolitan hematology unit may introduce other confounding factors such as socioeconomic status and treatment accessibility that limit generalizability to other healthcare settings and demographics. A systematic review analyzing outcomes in patients with MM using data from 84 previous publications from 37 countries highlighted that ethnicity, age, and socioeconomic factors impacted patient outcomes [22]. Furthermore, a Swedish nationwide registry study examining regional differences in survival outcomes found that patients with MM in one of six studied regions had significantly different outcomes, suggesting that local treatment guidelines may influence outcomes, even though national recommendations exist in Sweden [23, 24].

Our results demonstrate significantly superior PFS in cohort B at 2-6L, while the difference in OS was significant only at 2-4L, but not 5L and 6L. This may be attributed to the smaller sample sizes at later LOT (38 patients received 5L and 25 patients received 6L), or to more aggressive disease biology at later LOT, leading to faster disease progression. Additionally, patients who progressed at 5 or 6L often received salvage therapies that could extend OS without necessarily affecting PFS, further decoupling the two end-

points at advanced stages. Furthermore, the lack of statistically significant differences in PFS in our separate analysis of TCE patients compared to those not exposed may be related to our study design. We stratified patients into two groups according to whether they were TCE during any time point in their RRMM treatment journey, including ongoing LOT at the most recent relapse. Consequently, early treatment regimens may have been similar or even identical in both cohorts, leading to similar PFS. The difference in PFS then diverges when patients are TCE at later LOT, such as 4L. Moreover, our definition of TCE may have contributed to the difference in OS between TCE and non-TCE patients, as patients receiving additional LOT are more likely to be exposed to additional drug classes. To mitigate this, we compared survival within the same line LOT, rather than across entire patient groups.

The findings in our study highlight that RRMM patients relapsing after triple-drug class exposure represent a growing population with significant unmet needs. In addition, novel drugs introduced during the study duration, such as carfilzomib and venetoclax, may have impacted outcomes. However, our data collection did not allow further explorative analyses to confirm this hypothesis. Future research should focus on the integration of novel modalities such as bispecific antibodies and CAR-T cell therapy, alongside optimizing treatment sequencing of currently available drugs. Recently, in 2024, bispecific antibodies were approved and reimbursed for use in the RRMM setting in Sweden, as reflected in updated national guidelines [23]. Clinical trials have demonstrated a large survival benefit for patients with previous exposure to multiple classes of drugs and multiple relapses [25, 26]. These improved outcomes have been corroborated in recent reports from real-world cohorts [27, 28]. However, outcomes in large real-world cohorts remain to be studied in Sweden and the Nordic countries. Additionally, despite the promising outcomes after CAR-T cell therapies in RRMM, their use remains limited outside of clinical trials [29]. Furthermore, while both clinical trials and real-world evidence show vastly superior outcomes in RRMM patients using these novel immunotherapies, the timing of their use and treatment sequence need to be clarified in future studies, as well as assessment of their cost-effectiveness and the possibility to personalize RRMM treatment [8, 30].

In summary, this study of a real-world RRMM patient population at a Swedish tertiary hematology center indicated that the use of modern treatment options improves patient outcomes. Additionally, we observed improved survival in patients exposed to all three main drug classes in modern MM treatment: PI, IMiD, and anti-CD38 mAb. Although these findings demonstrate the survival benefits of current RRMM treatment, continued development of new treatments with novel mechanisms of action is needed to further improve the outcomes of our patients with MM, eventually bringing hope of a possibility to cure the disease.

Acknowledgments

We thank all participating patients, as well as the dedicated staff at our department whose tireless work made this research possible.

Funding

This study was supported by collaborative research funding from Pfizer Inc. We also wish to acknowledge the financial support from the Cancer Research Funds of Radiumhemmet; the Swedish Cancer Society; the Iris, Stig and Gerry Castenbäck Foundation for Cancer Research; and Vinnova (Sweden's Innovation Agency).

Disclosures

This study was approved by the Swedish Ethical Review Authority (ethical permit 2014/526-31/3 and 2019-04973) and was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

The authors declare no conflict of interest.

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