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No effect of older age on the severity and duration of alcohol withdrawal syndrome

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Objective. Few studies have analysed the impact of age on the severity and duration of Alcohol Withdrawal Syndrome (AWS), and the results are contradictory. We aimed to investigate the effects of age on the severity and duration of AWS during inpatient detoxification.

Methods. This study was a retrospective cohort study in the inpatient facility of Brijder Addiction Care, The Hague, the Netherlands. The total sample consisted of 141 patients with AWS: 59 patients aged < 55 years and 82 patients aged ≥ 55 years. Patients were treated with a standard detoxification protocol. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) was used to assess the severity and duration of AWS. Other outcome variables were the duration of hospital stay and the occurrence of delirium, falls, and seizures.

Results. The maximum CIWA-Ar score, first CIWA-Ar score, time to achieve a CIWA-Ar score < 10, and duration of hospital stay were not different between the age groups. The numbers of delirium, falls, and seizures were too small to test the statistical significance of the difference between age groups. In multivariate analyses adjusted for gender, units of alcohol used per day, somatic diseases, and benzodiazepine use, age (as a continuous variable) was neither associated with severity nor with duration of AWS.

Conclusions. Age was not a significant predictor of severity or duration of AWS in multivariate analyses.

Key words: age, alcohol withdrawal syndrome, detoxification

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INTRODUCTION

Alcohol-withdrawal syndrome (AWS) is common in alcohol-dependent patients who reduce or stop their alcohol consumption. The symptoms of alcohol withdrawal are numerous and vary between patients ^{1,2}. In most cases, alcohol withdrawal symptoms are mild to moderate and include anxiety, sweating, tremors of the hands, nausea, vomiting, and insomnia ³⁻⁵. Patients with mild or moderate AWS require little or no medication and do not need close monitoring. However, a minority of patients with AWS develop more severe symptoms that may be life-threatening and warrant additional medication as well as close monitoring in an inpatient facility. These more severe symptoms include hallucinations, seizures, and delirium tremens.

The prevalence of alcohol use disorders (AUD) in older age groups (50-69 and 70+) has remained relatively stable over the last 3 decades ⁶. However, due to the ageing of the general population in the European Union ⁷ and the United States ⁸, and a clear trend towards increased alcohol consumption in higher

age groups in the US (despite heterogeneity in survey results)⁹, it is likely that the number of older patients seeking treatment for AUD will increase, and therefore more knowledge of AWS in older adults is necessary.

A literature search on age as a predictor of the course and severity of AWS yielded only six studies. We searched the “EMBASE 1974 to Present” database, with a specific search strategy combining search terms related to alcohol detoxification or alcohol withdrawal syndrome with a range of search terms related to ageing or older age. This search yielded 70 references, five of which described studies that were relevant for our research question. Searching the reference list of these five articles yielded a sixth reference to a study on the association between age and alcohol withdrawal. A retrospective cohort study comparing a younger group of patients (aged 21–35, $n = 36$) with an older group of patients (aged 60 and above, $n = 48$) admitted to a hospital for alcohol detoxification, showed that AWS was more severe and lasted longer in the older age group¹⁰. The use of medication for AWS was similar in both groups.

Another retrospective cohort study investigated inpatients of an alcohol detoxification unit¹¹. No significant differences were found in initial and maximum scores on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA)¹², dose, or duration of medication use between patients younger ($n = 202$) and older ($n = 84$) than 60 years of age. Patients older than 60 had an increased risk of delirium and falling compared to patients younger than 60 years of age. With increasing age, the risk for a longer clinical stay and the risk for discharge to an extended care facility increased.

The first prospective cohort study, comparing a younger group of patients (aged 21–33, $n = 24$) to an older group of patients (aged 55–77, $n = 26$) admitted to an inpatient alcohol addiction treatment unit, found more severe AWS in the older group, and older patients required higher doses of medication compared to the younger age group¹³. Another prospective cohort study on the course of AWS was conducted in a general hospital without a designated ward for detoxification, and showed that patients aged 70 or older ($n = 55$) had a higher risk of developing seizures or delirium¹⁴. The third prospective cohort study on age and AWS was conducted in an inpatient detoxification ward in a university hospital and found no effect of age on the severity of AWS between groups of patients younger than 29 years of age ($n = 71$), between 30 and 59 years of age ($n = 611$) and older than 60 years of age ($n = 41$)¹⁵. Finally, a large combined retrospective ($n = 892$) and prospective ($n = 321$) study in an inpatient detoxification ward in a psychiatric hospital, including 50 patients older than 60 years, found no effect of age on the severity of AWS, the highest CIWA-A score, or the amount of medication used¹⁶. In sum, studies found contradictory results concerning the

effect of age on AWS. In addition, two studies^{11,14} found age to be a risk factor for some complications, but this was not the case in the other study¹⁵.

All studies that we found through our literature search were published more than 20 years ago, were limited by their small sample size of older patients (range: $n = 26$ –84), and the majority of studies did not use the CIWA, which is generally considered the gold standard of rating scales to assess AWS.

This study aimed to investigate the effect of age on the severity and duration of AWS in inpatients admitted for alcohol detoxification, both by comparing two age groups and with age as a continuous variable, adjusted for covariates (especially somatic comorbidity and benzodiazepine use). We hypothesised that higher age would be independently associated with a more severe and longer duration of AWS.

PATIENTS/MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURE

This was a retrospective observational cohort study using electronic medical records. The sample consisted of consecutively admitted patients to the inpatient detoxification facility of Brijder Addiction Care in The Hague, the Netherlands, with alcohol detoxification as one of the reasons for admission. Patients had to be 18 years of age or older, their last alcohol consumption should not have been longer than 72 hours prior to admission, and they had to have at least one CIWA-Ar score of ≥ 10 at some point during the detoxification period, indicating at least a moderate AWS. All eligible patients that were admitted from the beginning of July until the end of September 2016 were included in our study. To be able to study the effect of age with sufficient statistical power, from October to December 2016, we no longer included all consecutive eligible patients, but only patients aged ≥ 55 years. If patients were admitted more than once during the inclusion period, we used the data from the first detoxification period in which the inclusion criteria were met.

To differentiate older from younger patients, ≥ 55 years was chosen as the cut-off. This value was chosen because 55 years is often used as a cut-off in studies of psychiatric patients. According to the Dutch Medical Research Involving Human Subjects Act¹⁷, formal review by a Medical Ethics Committee was not required since this was a retrospective study with data already collected for clinical reasons; therefore, there was neither burden nor risk for the participants.

MEASURES

To measure alcohol withdrawal symptoms, the

CIWA-Ar¹² questionnaire was used. This is a ten-item scale with a maximum score of 67. Our hospital guidelines advised that CIWA-Ar scores should be determined every two hours until a score of < 10 is achieved. The primary outcome measure for severity of AWS was the maximum CIWA-Ar score during the detoxification period. A secondary outcome measure for severity was the first CIWA-Ar score. If the first CIWA-Ar score was < 10, we used the first CIWA-Ar score that was ≥ 10 , i.e., the CIWA-Ar score at AWS onset, because if the CIWA-Ar score increased after admission, the patient was probably intoxicated at admission. Another secondary outcome measure for severity was the occurrence of three types of complications: delirium, falls, and seizures. The primary outcome measure for the duration of AWS was the time in hours from the first measurement with a CIWA-Ar score ≥ 10 until remission of AWS, defined as the first time the CIWA-Ar score was < 10 without higher CIWA-Ar scores afterwards. If the last available CIWA-Ar score was ≥ 10 and < 15 and no benzodiazepines were given after the final CIWA-Ar score, we assumed that in these patients, experienced nurses assessed that AWS had remitted after the last CIWA-Ar measurement and did not perform further assessments with the CIWA-Ar. Both the authors of the revised CIWA-Ar¹² and the author of a meta-analysis¹⁸ recommended that benzodiazepine treatment for patients with CIWA-Ar scores between 10 and 15 should be based on clinical judgement and clinical needs of the patient. Based on this recommendation, we calculated an alternative, less strict remission variable in which a final CIWA-Ar score ≥ 10 and < 15 was also regarded as remission, in order to perform sensitivity analyses. A secondary outcome measure for the duration of AWS was the duration of the hospital stay in days. CIWA-Ar scores, the occurrence of complications (delirium, falls, and seizures), and the duration of hospital stay were extracted from the electronic medical records.

COVARIATES

The following variables were also extracted from the electronic medical records, in order to describe the sample: patients' demographics, somatic comorbidity (both history and present at admission), somatic comedication, psychiatric comorbidity (presence of other DSM-IV diagnoses than substance use disorders), units of alcohol used per day prior to admission, illicit drug use prior to admission, admission laboratory data, benzodiazepine use, and other psychotropic medication use (e.g., antipsychotics and antidepressants). The number of somatic diseases was not normally distributed, therefore, we created 3 groups based on the number of somatic comorbid diseases (0, 1-2, or ≥ 3).

The total amount of benzodiazepine used was converted into diazepam equivalents. In some cases,

benzodiazepines were already used prior to admission or were used for other reasons than alleviating alcohol withdrawal symptoms; e.g., sleeping medication or anxiety medication. Whenever it was possible to make this distinction, only benzodiazepines used for AWS were counted.

TREATMENT PROTOCOL

Depending on the initial CIWA-Ar score, a pre-specified amount of a benzodiazepine is given to reduce AWS symptoms. A score of < 10 is considered low, and no medication is given. A score of 10-19 is considered moderately severe, and a single dose of medication is given. A single dose is defined as 10 mg of diazepam, 25 mg of chlordiazepoxide, 2.5 mg of lorazepam, or 50 mg of oxazepam. A score of ≥ 20 is considered severe, and a double dose of medication is given. After the initial CIWA-Ar score, the CIWA-Ar should be administered every 2 hours, and the medication dose is adjusted accordingly.

STATISTICAL ANALYSES

Baseline demographical and clinical characteristics were compared between older (≥ 55 years) and younger (< 55 years) patients using chi-squared tests or Fisher's exact tests for dichotomous data, independent t-tests for continuous variables if data were normally distributed, and Mann-Whitney U tests if continuous variables were non-normally distributed¹⁹. To analyse univariate differences between older and younger patients in the maximum and first CIWA-Ar scores, time until CIWA-Ar was < 10, and duration of hospital stay, Mann-Whitney U tests were used. The association of age (as a continuous variable) with the primary severity outcome, maximum CIWA-Ar score, was analysed using linear regression, corrected for gender and number of alcohol units used daily before admission. These analyses were repeated with corrections for the number of somatic diseases and the total amount of benzodiazepines used during detoxification. These covariates were chosen because they are likely to be associated with age as well as with the course of AWS. The association of age (as a continuous variable) with the primary duration outcome, time until the CIWA-Ar score was < 10 was analysed using Cox regression, with the same corrections for covariates as the linear regression analyses. The Cox regression analyses were repeated with the less strict remission variable (final CIWA score < 15 with no benzodiazepines afterwards). A p-value < .05 was considered statistically significant. Statistical analysis was done using IBM SPSS Statistics for Windows, Version 27.

RESULTS

A total of 141 patients admitted from July to December

2016 met the inclusion criteria: 82 younger patients (< 55 years) and 59 older patients (≥ 55 years). Table I presents the demographic and clinical characteristics of the two age groups. Older patients had significantly more somatic diseases and used more somatic medication than younger patients. There were no statistically significant differences between the two age groups in any of the other demographic and clinical characteristics. There were no statistically significant differences in gamma-glutamyl transferase (GGT), aspartate-aminotransferase (ASAT), or alanine-aminotransferase (ALAT) between older and younger patients (data not shown in Table I).

UNIVARIATE ANALYSES OF AGE

Table II presents the univariate analyses of severity and duration of AWS (with CIWA-Ar < 10 as the cut-off score) in the two age groups.

The maximum CIWA-Ar score, first CIWA-Ar score ≥ 10 , time to achieve a CIWA-Ar score < 10 and duration of hospital stay did not differ significantly between younger and older adults with AWS. Three (5.1%) of the older patients had had a delirium, three (5.1%) had fallen, and none had had seizures. Of the younger patients, none had

had a delirium, one (1.2%) had fallen, and one (1.2%) had had a seizure. No patient had more than one complication. These numbers were too small to test the statistical significance of differences between the age groups.

MULTIVARIATE ANALYSES

In multivariate analyses, we first analysed the effect of age, corrected for gender and the units of alcohol used per day prior to admission, on the maximum CIWA-Ar score in patients with AWS. The results are presented in Table III. Age was not significantly associated with the maximum CIWA-Ar score, but female patients and patients who used more units of alcohol per day before admission had significantly higher maximum CIWA-Ar scores. Adding the number of comorbid somatic diseases and, finally, the amount of benzodiazepine used during the detoxification period yielded similar results. In the model with adjustment for benzodiazepines, having more than two comorbid somatic diseases was associated with a lower maximum CIWA-Ar score. The dose of benzodiazepines used during the detoxification period was associated with a higher maximum CIWA-Ar score.

Table I. Baseline characteristics of study participants (n = 141).

Variable	Younger < 55 (n = 82)	Older ≥ 55 (n = 59)	Statistic	p-value
Age, mean (SD)	45.2 (7.9)	60.2 (4.6)	n.a.	n.a.
Female gender, n (%)	27 (32.9)	25 (42.2)	$\chi^2 = 1.315$ (df = 1)	.251
History of				
Delirium, n (%)	10 (12.2)	8 (13.6)	$\chi^2 = .057$ (df = 1)	.811
Seizure, n (%)	22 (26.8)	17 (28.8)	$\chi^2 = .068$ (df = 1)	.795
Liver disease, n (%)	8 (9.8)	9 (15.3)	$\chi^2 = .978$ (df = 1)	.323
Epilepsy, n (%)	1 (1.2)	3 (5.1)	Fisher's exact test	.309
DSM IV Axis I disorder ^a , n (%)	39 (47.6)	26 (44.1)	$\chi^2 = .168$ (df = 1)	.681
DSM IV Axis II disorder, n (%)	28 (34.1)	16 (27.1)	$\chi^2 = .789$ (df = 1)	.374
Use of				
Benzodiazepines, n (%)	17 (20.7)	17 (28.8)	$\chi^2 = 1.225$ (df = 1)	.268
Cannabis, n (%)	12 (14.6)	5 (8.5)	$\chi^2 = 1.228$ (df = 1)	.268
Amphetamine, n (%)	2 (2.4)	1 (1.7)	Fisher's exact test	1.00
Opioids, n (%)	7 (8.5)	3 (5.1)	Fisher's exact test	.521
Cocaine, n (%)	8 (9.8)	2 (3.4)	Fisher's exact test	.193
Psychotropic medication, n (%)	32 (39.0)	27 (45.8)	$\chi^2 = .640$ (df = 1)	.424
Units of alcohol used/day prior to admission, median (IQR)	21 (14-28)	17.5 (12-24)	U = 1802	.084
Somatic diseases, median (IQR)	0 (0-2)	2 (1-3)	U = 3412	< .001
Somatic medication, median (IQR)	1 (0-3)	2 (0-6)	U = 3209	< .001

n.a.: not applicable; df: degrees of freedom; n: number; SD: standard deviation; IQR: interquartile range; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV;

^a comorbid psychiatric diagnoses (other than substance use disorders).

Table II. Univariate analyses of the association between age and severity and duration of Alcohol Withdrawal Syndrome (n = 141).

Variable, median (IQR)	Younger (n = 82)	Older (n = 59)	Mann-Whitney U	p-value
Maximum CIWA-Ar score, median (IQR)	18 (13-22)	16 (13-21)	U = 2087	.164
First CIWA-Ar score $\geq$ 10, median (IQR)	13 (11-17)	12 (11-15)	U = 2133	.224
Time until CIWA-Ar < 10, hours, median (IQR)*	18 (10-32)	23 (11-32)	U = 533	.567
Duration of hospital stay, days, median (IQR)	11 (7-16)	16 (10-25)	U = 2762	.150

CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol, Revised; IQR: interquartile range.

*time until CIWA-Ar < 10 only calculated for those who achieved a CIWA-Ar <10; n = 40 younger patients and n = 29 older patients.

Table III. Linear regression analyses of maximum CIWA-Ar score in patients with AWS (n = 134).

	Model 1		Model 2		Model 3	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Age	-0.045 (-0.143-0.052)	.359	-0.013 (-0.121-0.095)	.811	0.055 (-0.014-0.124)	.118
Female gender	2.864 (0.837-4.890)	.006	2.877 (0.848-4.906)	.006	2.172 (0.882-3.462)	.001
Units of alcohol used/day (prior to admission)	0.189 (0.092-0.286)	< .001	0.191 (0.094-0.289)	< .001	0.083 (0.020-0.147)	.011
1-2 somatic diseases ^a			-0.326 (-2.608-1.956)	.778	0.356 (-1.094-1.805)	.628
> 2 somatic diseases ^a			-1.864 (-4.680-0.951)	.193	-2.032 (-3.817- -0.248)	.026
Total dose of benzodiazepines					0.078 (0.067-0.089)	<.001

^a Reference group: no comorbid somatic diseases; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol, Revised; B: unstandardized coefficient B; CI: confidence interval; p: p-value.

Model 1: corrected for gender and daily use of alcohol; Model 2: corrected for gender, daily use of alcohol and comorbid somatic diseases; Model 3: corrected for gender, daily use of alcohol, comorbid somatic diseases, benzodiazepine use.

Table IV. Cox regression analysis of time until CIWA-Ar < 10 in patients with AWS (n = 123).

	Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	1.019 (0.991-1.049)	.188	1.022 (0.990-1.055)	.186	1.005 (0.972-1.038)	.785
Female gender	1.028 (0.610-1.732)	.917	1.034 (0.610-1.753)	.902	1.107 (0.640-1.916)	.717
Units of alcohol used/day (prior to admission)	1.001 (0.977-1.026)	.941	1.001 (0.977-1.026)	.939	1.022 (0.996-1.048)	.096
1-2 somatic diseases ^a			1.046 (0.565-1.937)	.887	1.108 (0.594-2.067)	.748
> 2 somatic diseases ^a			1.133 (0.546-2.354)	.737	1.204 (0.541-2.681)	.650
Total dose of benzodiazepines					0.979 (0.972-0.986)	< .001

^a Reference group: no comorbid somatic diseases; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol, Revised; HR: Hazard ratio; CI: confidence interval; p: p-value.

Model 1: corrected for gender and daily use of alcohol; Model 2: corrected for gender, daily use of alcohol and comorbid somatic diseases; Model 3: corrected for gender, daily use of alcohol, comorbid somatic diseases, benzodiazepine use.

Table IV presents the results of the Cox regression analyses of the time until the CIWA-Ar score was < 10, in patients with AWS. In the first model, we corrected only for age, gender, and units of alcohol used per day prior to admission. None of these variables was significantly associated with time until the CIWA-Ar score was < 10. In the second model, the number of comorbid somatic diseases was added, and in the third model,

the total amount of benzodiazepines used during detoxification was added. In both additionally corrected models, the number of comorbid somatic diseases had no significant effect on time until the CIWA-Ar was < 10. The total amount of benzodiazepines used during detoxification was associated with a shorter time to remission: HR = 0.979, 95% CI = 0.972-0.986, $p < .001$. Repeating these analyses with the less strict remission

variable (CIWA-Ar score < 15) yielded similar results, except that in the second model, with adjustment for the number of somatic diseases, age was associated with a slightly longer time till remission (HR = 1.024, 95% CI = 1.000-1.048, $p = .048$). After adjustment for the total amount of benzodiazepines, this association was no longer significant.

DISCUSSION

To the best of our knowledge, based on the literature search we described in the Introduction, this is the first study that investigated the association between age and AWS, corrected for confounders. Older patients, aged ≥ 55 years, with AWS ($n = 59$) had a maximum CIWA-Ar score, first CIWA score, time until CIWA-Ar was < 10, and duration of hospital stay that were not significantly different from those of younger patients with AWS (aged < 55 years, $n = 82$). In multivariate analyses with age as a continuous variable, we found no association of age with the severity or duration of AWS either. These findings contradict the oldest studies on this topic^{10,13}, but are in line with the more recent studies^{11,15,16}. Both older studies were limited by their small sample sizes (older patients, $n = 26$ and $n = 48$, respectively). In addition, the two older studies dichotomized patients into two very different age groups, excluding patients aged 35-58, which may increase the risk of a false positive result. Our results are in line with both other studies that also analysed age as a continuous variable^{15,16}.

We unexpectedly found that female patients had a significantly higher maximum CIWA score than male patients, but gender did not have a significant effect on the duration of AWS. Only one study used gender as an independent variable and reported that gender had no statistically significant influence on the occurrence of severe AWS¹⁵. A meta-analysis of predictors of severe AWS found that gender did not predict AWS, but the question of whether this may be different in older patients can only be answered by studies replicating our results²⁰.

We found that the total dose of benzodiazepines used during detoxification was positively associated with the maximum CIWA-Ar score, which is consistent with the idea that more benzodiazepines will be used in cases of more severe AWS. However, in our multivariate analyses, the amount of benzodiazepines used was associated with a shorter duration of AWS, demonstrating that the administration of more benzodiazepines will result in a shorter duration of AWS. Whether or not the association between AWS and age or somatic comorbidity should be corrected for the use of benzodiazepines, which may also lead to overcorrection,

remains debatable, and therefore we presented our main outcome with and without correction for the use of benzodiazepines. Only Kraemer et al.¹¹ considered both aspects of benzodiazepine use in relation to AWS and found that adjusting their multivariate analyses for the use of scheduled benzodiazepine did not change their result that age had no significant influence on AWS. However, they did not correct for the dose of benzodiazepine use, and it is not clear why they only corrected for whether the patients received scheduled benzodiazepines. Our analysis of the use of benzodiazepines was complicated by the use of benzodiazepines at baseline. Although we tried to make a distinction between benzodiazepines used for AWS and other reasons (sleep medication, anti-anxiety medication), it is unclear to what degree this was successful, as a clear registration of the indication for benzodiazepine use was sometimes missing in the medical records. Our study did not demonstrate statistically significant differences between younger and older patients regarding complications (delirium, falls, or seizures) because of the low prevalence of complications in our study group. Limitations of our study were the retrospective design based on chart reviews, which resulted in a limited number of variables that could be included in the study. We lack, for example, information about the severity of AUD, age of onset, and the number of times each patient was previously treated for alcohol withdrawal. For various reasons – patients were sleeping, there was a lack of time of nursing staff – two-hourly measurements of AWS were not always possible, which is inevitable in a retrospective study of data collected in daily practice. The CIWA-Ar scores were rated by many different nurses, with unknown inter-rater reliability. However, all nurses were experienced raters. It is possible that the CIWA-Ar lacks sensitivity for AWS in older adults. The CIWA-Ar is considered the gold standard for AWS, but the lack of studies validating different cut-offs for the CIWA-Ar or other AWS rating scales in older patients is a limitation. The slightly different time frame to include younger (3 months) versus older adults (6 months) may be a limitation, but it was chosen to include more older adults. Our sample of older patients may represent a selection of those who remained healthy, with patients with severe AUD having already died. Our subgroup of older patients was relatively young and had a relatively low number of somatic diseases; this may limit the generalizability of our results to very old or frail patients.

CONCLUSIONS

We conclude that we could not demonstrate an influence of age on the severity or duration of AWS after

correction for confounders. Prospective research with strict guidelines for CIWA-Ar measurements is recommended to reach a more comprehensive understanding of the role of age and somatic comorbidity in AWS.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

RMK: designed the study, supervised the data collection and drafted the manuscript; CY, FtW: collected the data and assisted with writing the manuscript; JFvdB: performed the statistical analyses and critically reviewed and revised the manuscript.

Ethical consideration

According to the Dutch Wet medisch-wetenschappelijk onderzoek met mensen (WMO; Medical Research Involving Human Subjects Act, 2022), formal review by a Medical Ethics Committee was not required since this was a retrospective study with data already collected for clinical reasons, therefore there was neither burden nor risk for the participants.

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