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► To cite this version:

Claire Villeneuve, Annick Rousseau, Jean-Phillipe Rerolle, Lionel Couzi, Nassim Kamar, et al.. Adherence profiles in kidney transplant patients: Causes and consequences. Patient Education and Counseling, 2020, 103 (1), pp.189 - 198. 10.1016/j.pec.2019.08.002 . hal-03488791

HAL Id: hal-03488791

<https://hal.science/hal-03488791>

Submitted on 21 Jul 2022

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Adherence profiles in kidney transplant patients: causes and consequences.

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A. Rousseau and C. Villeneuve participated in data analysis and manuscript writing.

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JP. Rerolle, M. Essig, L. Couzi, N. Kamar, I. Etienne, PF. Westeel, M. Büchler, L. Esposito and A. Thierry participated in the clinical trial.

Disclosure: The authors declare no conflicts of interest.

Funding:

The EPIGREN trial was supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interregional 2006), the Direction de la Recherche et de l'Innovation, Limoges University Hospital, the French Medicine Agency and the Agence de Biomédecine.

Abbreviations:

C₀, trough concentrations

CHU Limoges, Centre Hospitalier Universitaire de Limoges

MCS-SF36, mental composite score of the 36-Item Short Form Health Quality Of Life Survey (SF-36)

MMAS-4, Morisky-Green-Levine Medication Adherence Scale

PRO, Patient Reported Outcomes

SD, Standard deviation

WHO, World Health Organization

Abstract

Objective: Adherence is a dynamic phenomenon and a critical determinant of transplant patients outcome. The objective of this longitudinal study was to explore adherence in kidney transplant patients followed-up for up to three years after transplantation.

Methods: Adherence was repeatedly estimated using the Morisky-Green-Levine 4-Item Medication Adherence Scale, in two successive cohorts of 345 (EPIGREN) and 367 (EPHEGREN) kidney transplant recipients. Mixed effect modeling with latent processes and latent classes was used to describe adherence time-profiles.

Results: Two latent classes were identified. The adherent class represented 85% of the patients. Patients of the poorer-adherence class displayed a lower adherence at one month ($p < 10^{-3}$), which worsened over time. Good adherence was associated with age > 50 years, fewer depression episodes (5% vs. 13%, $p = 0.001$) and a better mental health component of quality of life (MCS-SF3647 \pm 11 vs. 41 \pm 13, $p = 0.015$). Survival without acute rejection episodes was longer in the adherent class ($p = 0.004$).

Conclusions: The risk of poor adherence in renal transplant patients can be detected as early as one month post-transplantation, using appropriate and easy tools adapted to routine monitoring.

Practice Implications: An early focus on vulnerable patients should allow putting into place actions in order to reduce the risk of poor outcome related to poor adherence.

1. Introduction

Adherence is a major issue for clinicians, policy-makers and health managers [1]. Given the strong negative impact of non-adherence on the health of patients with chronic diseases, the WHO declared that improving therapeutic adherence was as crucial as improving the therapeutic arsenal and strategies [1-4]. In transplantation, the association of non-adherence between late rejection and graft loss [5, 6] renders it a critical determinant of patient outcome. The reported prevalence of non-adherence in transplant patients ranges between 15% and 30%, depending on the transplanted organ. This variability also relates to the various methods of evaluation used [7-20]. Indeed, given the absence of a gold standard, adherence is assessed using questionnaires, immunosuppressive drug trough concentrations, pill counts or electronic pill dispensers. Among the available questionnaires, the Morisky-Green-Levine Medication Adherence Scale (MMAS-4), a self-reported medication-taking behavior scale, has been widely used in renal transplantation [21].

Adherence is mainly influenced by patient-related or social factors and drug regimen factors. Among them all, age, quality of life, depression and adverse events have been largely reported to influence adherence in transplant patients [1-3, 5-9, 11-14, 16, 22, 23]. However, most studies exploring the risk factors of non-adherence had a transversal design, where adherence was evaluated only once. However, adherence is a dynamic and time-dependant behavior, and non-adherence can be either isolated or repeated over time, with different causes and consequences on patients outcomes. Consequently, some authors have argued that a longitudinal design is better adapted for adherence studies [11, 24, 25]. Chrisholm *et al.* [26] considered patients as non-adherent only when they missed doses repeatedly, while Massey *et al.* [11, 24] argued for longitudinal studies, taking into account the adherence

behavior changes over time. To our knowledge, only one longitudinal study in transplantation considered repeated assessments of adherence using generalized estimating equations [5].

In this context, we considered that a longitudinal study of non-adherence, its causes and consequences in transplant patients, was necessary. Therefore, the main objective of the present study was to describe the evolution of adherence over time. The secondary objectives of this study were to explore the factors associated with poor adherence and the relationships between adherence and patients outcomes. Such a complex study had to be compliant with the following constraints: i) taking into account the non-gaussian distribution of the MMAS-4 score and describing the latent process of the psychometrics score [27-29] ; ii) taking into account the inter- and intra-patient variability; iii) allowing the identification of different adherence profiles (subgroups); iv) including covariates in the analysis.

2. Materials and Methods

2.1. Design and study population

We analyzed data collected prospectively in adult *de novo* kidney transplant recipients enrolled in two successive, multicenter prospective cohort studies called “EPIGREN”, conducted between 2007 and 2011 in 3 kidney French transplantation centers [30] and “EPHEGREN”, conducted between 2012 and 2017 in the same centers plus 4 others. These studies were sponsored by CHU Limoges and complied with the legal requirements of the Declaration of Helsinki. They received approval and authorization from the regional Ethics Committee (n°06-040 on 05/19/2006 for EPIGREN and n°130-2013-30 on 11/20/2013 for EPHEGREN), the French Medicine

Agency (n°060566 on 08/08/2006) and the National Committee for Informatics and Liberties (907275 ACT in 2006 for EPIGREN, 912242 ACT in 2012 for EPHEGREN). All *de novo* patients followed-up in the participating centers were eligible, except if they did not understand the protocol, or were not able to understand written French. Patients received information about the study during a routine consultation and were enrolled by a nephrologist, only after giving their written consent, and before the end of the first month post-transplantation. Study visits were defined as follows: one month (M1), M3, M6, M12, M18, M24, and M36 after transplantation. Patients in the EPIGREN cohort benefited from two extra visits, at M9 and M30. Immunosuppressive regimens complied with the standard of care for transplanted patients (tacrolimus or cyclosporine, the dose being adjusted on trough blood concentrations -C₀- combined with mycophenolate).

2.2. Data collection

To be included in the present study, the patients had to have filled in the patient reported outcomes (PRO) forms on at least 2 occasions.

PRO were collected from self-administered questionnaires at each study visit by a clinical research assistant (table 1). Adherence was evaluated using the MMAS-4 [21], where a score of 0 indicates good adherence and a higher score indicates lower adherence. Consequently, the patients with a score=0 were considered to be adherent and non-adherent with a score>0 [31]. Health-related quality of life was evaluated using the 36-item short-form health survey (SF-36) [32]. Finally, patients could declare adverse events using a dedicated list (table 1) [30, 33-36]. For each reported adverse event, patients could score the level of the induced discomfort, from 1 (no discomfort) to 5 (very high discomfort), which were dichotomized as ≤ 2 vs. > 2 [30] for the purpose of this study.

Clinical data (including acute rejection episodes) and calcineurin inhibitors concentrations were collected from medical records on a clinical research form (table 1). Cyclosporine $C_0 < 80 \mu\text{g/L}$ and tacrolimus $C_0 < 5 \mu\text{g/L}$ were considered to be subtherapeutic [37, 38] for the purpose of this study.

2.3. Statistical analysis

2.3.1. Description of the study population

Statistical analysis was performed using R version 3.0 [39]. Categorical data were reported as frequency and percentage and continuous data as mean \pm standard deviation. Intra-patient coefficients of variation of calcineurin inhibitors C_0 were calculated.

2.3.2. Adherence time-profiles modeling

2.3.2.1. Elaboration of the model

The model describing adherence profiles was elaborated using the 24-month follow-up data of the EPIGREN cohort (development dataset). Adherence time-profiles after transplantation were analyzed using mixed models with latent process and latent classes, implemented in the *lcmm* R package [40]. A model with latent process displays two components: (i) a measurement model, which links a latent variable with the variable of interest using a link function; (ii) a structural model which describes the time-profiles of the latent variable of interest, *i.e.* which defines subgroups (classes) that display similar time-profiles. In the structural model, the inter-patient latent variable heterogeneity is investigated using a mixed model with latent classes. The final model is then built by screening and selecting significant covariates and adding them to the structural model. Here, the latent variable of interest was

adherence measured by the MMAS-4. As the distribution of the MMAS-4 is non-Gaussian, the link function was selected in order to transform it into a Gaussian latent variable. The structural model described classes with similar adherence time-profiles, and the final model included covariates associated with adherence time-profile classes.

The best base model was selected based on maximum likelihood and highest posterior probability, assuming that missing data are missing at random. The goodness-of-fit of the selected model was assessed using graphical methods. The same approach was then used to screen and select significant covariates and add them to the structural model.

2.3.2.2. Validation of the model

The validation of the model was performed in three steps, by comparing the classification of the patients in latent classes using different datasets vs. their classification using 24-months post-transplantation data, which was considered to be the reference for the validation. Firstly, the reliability of the model was evaluated by comparing the classification of the patients in the latent classes using only the first 6 months data; the sensitivity and specificity of the model when using 6 months post-transplantation data only was determined. Secondly, the consistency of the model was evaluated on its ability to classify patients in their latent class using 36-months follow-up data, and was expressed by its sensitivity and specificity when using 36-months post-transplantation data. Finally, the model was validated using an independent dataset (*i.e.*, validation dataset), corresponding to patients enrolled in the EPHEGREN cohort. Its accuracy and robustness were evaluated on its ability to classify patients in the appropriate adherence latent classes, estimated using the

maximum likelihood and highest posterior probability, and graphically by checking its goodness-of-fit.

2.3.3. Factors associated with adherence profiles

The exploration of factors potentially associated with adherence profiles was performed in the EPIGREN dataset by comparison between the latent classes, using the Pearson chi-square test for categorical data and the one-way Anova or the t-test for continuous data. The Bonferroni risk correction was applied in the case of multiple comparisons. The Pearson's coefficient test was used to evaluate linear correlation between quantitative variables. Two-sided p-values <0.05 were considered to be statistically significant.

2.3.4. Relationship between adherence profile and patient outcomes

The association between adherence latent classes and rejection-free survival was evaluated in both cohorts. Time-to-rejection was estimated using Kaplan-Meier analysis and the latent classes were compared using the log-rank test.

3. Results

3.1. Description of the population

Three hundred and forty five of the 350 (98.6%) patients enrolled in the EPIGREN cohort and 367 of the 383 patients (95.8%) enrolled in the EPHEGREN cohort were included in the analysis. The main socio-demographic and clinical characteristics of the two populations are summarized in table 2. Less than 10% of the patients were lost-to-follow-up before the end of the study (Figure 1). Overall, 1603 and 2296 self-administered questionnaires were collected in the two cohorts. The majority of patients (89,9% and 97.5% respectively) filled out the questionnaires at least 4 times during their follow-up (table 3).

The most prescribed immunosuppressive strategy at M1 was the association of mycophenolate mofetil and tacrolimus BID (approximately 75% of the patients of both cohorts).

At M1, respectively 6.8% and 4.8% of the patients of EPIGREN and EPHEGREN were considered to be non-adherent. Among them, only one patient in each cohort had a MMAS-4 score of 3, on one occurrence. Adherence rates at each period for both cohorts are presented in table 3. Non-adherence increased progressively over time, to reach 20.5 % in EPIGREN and 13.1% in EPHEGREN at 2 years post-transplantation (table 3). Non-adherence was mostly qualified as “being careless at times about taking the medicine” (in respectively 215 and 124 cases) and “forgetting to take the medicine” (in respectively 172 and 141 cases).

3.2. Modeling of adherence time-profiles

3.2.1. Elaboration of the model

The link function selected for the measurement model was a quadratic I-spline transformation with 3 manual nodes dividing the patients into two latent classes, adherent and non-adherent. The best structural model describing adherence over time was a linear function. The final model included diarrhea ($p=0.021$) and recipient age (age>50 vs. ≤ 50 years, $p=0.00004$) (figure 2). The model allowed classifying subjects unambiguously in their latent class (table 4) and the specific predicted trajectories demonstrated a very good fit with the measured longitudinal data (figure 3).

3.2.2. Validation of the model

The good reliability of the model was evidenced when using the EPIGREN follow-up data until M6: *a posteriori* classification was overall adequate in 319/345 (92.5%)

patients, and the model displayed a sensitivity of 75.0% and a specificity of 95.5% when using 6-months follow-up data.

Good consistency was also observed, despite numerous missing data, with a satisfactory *a posteriori* classification in 341/345 (98.8%) patients, corresponding to a sensitivity of 92.3% and a specificity of 98.6% when using 36-months follow-up data.

The model applied to the independent EPHEGREN cohort (validation dataset) demonstrated its ability to classify patients in the appropriate adherence latent classes, evidenced by satisfactory maximum likelihood, *a posteriori* classification performance and goodness-of-fit (figure 4).

3.3. Factors associated with adherence profiles

Almost eighty five percent of the patients of the EPIGREN cohort (293/345) were classified *a posteriori* in the latent class of good adherence, while the proportion of patients classified in the adherence latent class was 91.8% in the EPHEGREN cohort (337/367, $p=0.004$). Adherence remained stable in the class of adherent patients while it worsened with time in the class of non-adherent patients (table 4, figure 2).

Recipient age was highly predictive of latent class membership, a younger age (≤ 50 years) being predictive of belonging to the non-adherent latent class. Even though taking into account diarrhea episodes improved the predictivity of the latent class model, the proportion of patients with diarrhea episodes did not significantly differed between the two classes (table 5).

In the non-adherent latent class, patients presented more episodes of non-adherence over time, and at M1 reported significantly more depressive syndromes (13% vs. 5% $p=0.001$) and a lower quality of life (MCS-SF36 41 ± 13 vs. 47 ± 11 , $p=0.015$) (table 5). The proportion of patients who experienced infections or adverse events did not differ between the 2 classes (table 4). No association was found between the proportion of

subtherapeutic C_0 and the adherence latent classes, neither for cyclosporine nor tacrolimus, and no patients were found to have subtarget drug concentrations and a MMAS-4 score >0 at the same visit. Consistently, the intra-patient coefficient of variation of C_0 was not associated with adherence for either molecules (table 6).

3.4. Adherence profile and outcomes

Kaplan Meier analysis demonstrated a significantly shorter period of time before the first episode of acute rejection in patients of the non-adherent latent class. Patient survival without rejection at 3 years was significantly lower in the non-adherent vs. the adherent class (72.7% vs. 88.6%, $p=0.004$) (figure 5).

4. Discussion and conclusion

4.1. Discussion

This is the first study describing the evolution of adherence to immunosuppressants over time in kidney transplant recipients using longitudinal mixed effects modeling.

In this study, MMAS-4 could be used to measure non-adherence thanks to its previous validation in a subset of EPIGREN patients, obtained by triangulation vs. immunosuppressant trough concentrations and face-to-face interviews with a trained pharmacologist [35].

The main strength and originality of this study is the longitudinal approach used for the exploration of adherence. The observations made in patients who missed visits or who were followed-up for different durations could be included in the analysis without precluding result interpretation, owing to the mixed effects modeling method employed. Most of the previously published studies in transplant patients were cross-sectional, with adherence evaluated at a single instance [6, 9, 12, 19]. Such studies do not allow considering the sequence of events over time. Moreover, with this type

of design, patients who only miss a single dose prior to the evaluation can be considered as non-adherent, while their adherence could be good afterwards. Plus, a single episode of non-adherence has neither the same causes, nor the same impact on patient outcome as repeated episodes, justifying the greater relevance of longitudinal studies. Among the few studies with a longitudinal design [5, 7, 11, 14, 24], De Geest *et al.* estimated the magnitude and evolution of non-adherence using logistic regression with parameters estimated by generalized estimating equations [5]. However, this type of test neither permits the investigation of a time-effect, nor the exploration of population heterogeneity.

Our approach allowed characterizing the magnitude and shape of adherence profiles over time, and identified 2 subpopulations of patients: a main group (85% of the patients) with a better and more stable adherence profile, and a smaller group with poorer and more variable adherence and a number of non-adherence episodes increasing over time. This is consistent with the findings of Nevins *et al.*, where two groups of patients with different adherence profiles were described: one group with a stable adherence profile and the other with an early and increasing non-adherence [41]. In our study, the rate non-adherence episodes increased over time, from less than 10% during the first month to 15-20% at the end of the third year. These results are consistent with previous studies [5, 7, 9-11, 41, 42], where a continuously increasing proportion of non-adherent patients over time was reported, up to 34.6% at 24 months in the study conducted by Massey *et al.*[11]. The differences in the prevalence of non-adherence reported between studies may partially be explained by the different methods of evaluation used [20].

Owing to the good sensitivity of our model, 75% of patients with non-adherence profiles could be detected as early as the first month post-transplantation.

Furthermore, its excellent specificity allowed discriminating early patients who later displayed multiple non-adherence episodes from those who reported occasional episodes. These results suggest that most patients with non-adherence profiles can be detected early on, and that adherence should be evaluated iteratively over time, in particular, in patients initially regarded as adherent. Overall, the good predictive performances of our model could help to identify patients at risk of poor adherence and in whom educative actions may be reinforced.

In this study, younger patients had a higher risk of poor adherence. Moreover, patients who reported more frequently depression episodes or a lower mental health-components of quality of life had a higher risk of poor adherence.

Interestingly, the proportion of non-adherent patients was lower in the EPHEGREN than in the EPIGREN cohort. This is consistent with the demographic characteristics of the cohorts: the patients were comparable in both cohorts except for age, which was higher in the EPHEGREN cohort (table 1). Of note, age increase between the two cohorts is consistent with the demographics of renal transplant patients in France [33]. The greater proportion of patients with good adherence in the EPHEGREN cohort could also be related to the initiation of patient therapeutic education programs between the end of EPIGREN and the beginning of EPHEGREN: the French law on public health published in 2009[43] rendered these programs mandatory for the management of patients with chronic diseases. Overall, educative actions may have a positive impact on depression and mental health component of quality of life, on the perception and the management of adverse events as diarrhea and consequently, on adherence. In this context, early educational activities could be set up systematically in patients at-risk: young patients, highly qualified patients, or those suffering from symptoms of depression or with a lower mental health component of quality of life.

Several studies have reported an association between non-adherence and adverse events, living alone, and immunosuppressive regimen [6-8, 44-53]. A young age is a well-known risk factor of poor adherence and psychological determinants of adherence have been widely studied [5, 7, 9, 11, 12, 14, 19, 42, 54-56]. Among them, depression has been reported to increase the risk of non-adherence. Studies on the relationship between quality of life and adherence showed contradictory results [8, 19, 54-60]. As underexposure to immunosuppressants after kidney transplantation is a well-known risk factor of biopsy-proven acute rejection [61] and could be the result of a poor adherence behavior, we investigated the potential relationship between adherence and immunosuppressive drug concentrations or intra-patient variability and found none. Drug concentrations generally remained in the target concentration. Still, a significantly longer survival without acute rejection episodes was observed in the adherent subgroup. Our hypotheses are that: (i) even though adapted to detect obvious non-compliance episodes (through undetectable trough concentrations), CNI trough blood levels may not be able to detect all types of non-adherence profiles adequately; (ii) patients complying more closely with their prescriptions a few days before planned blood sampling and consultations. These hypotheses are consistent with the observation made by Scheel *et al.* that despite the association of acute rejection with both the variability of immunosuppressant exposure -particularly subtherapeutic trough concentrations- and patient reported adherence, these factors were not associated with each another [62].

Unfortunately, the lack of pre-transplantation data prevented us from exploring potential pre-transplant risk factors for poor adherence. Previous studies reported that pre-transplant non-adherence may be associated with non-adherence at 6 months post-transplantation and beyond [5, 13]. Further studies investigating the

relationships between pre-transplantation risk factors, adherence after transplantation, immunosuppressive drug exposure and long-term outcome are still necessary in order to, if relevant, set up pre-transplant interventions to limit the risk of poor adherence after transplantation.

4.2. Conclusion

In this study, a longitudinal approach based on mixed effects modeling allowed describing the evolution of adherence to immunosuppressants over time in kidney transplant patients. Two subpopulations of patients were identified: a subpopulation with good and stable adherence and a subpopulation with poor and variable adherence, deteriorating over time.

Overall, non-adherence behavior is detectable early on in the majority of patients. Nevertheless, adherence should be evaluated regularly over time, in all patients to identify potential non-adherence issues and set-up appropriate actions.

4.3. Practice Implications

Characterizing patient adherence profiles early on should be performed in order to identify the barriers to adherence, propose adapted therapeutic educational programs. Characterizing adherence regularly afterwards may help prevent the multiplication of non-adherence episodes in patients with a poor adherence profile early on, as well as the occurrence of non-adherent episodes in patients initially considered to be adherent, by organizing individualized and targeted interventions.

Furthermore, the improvement of patient care should include not only drug regimen optimisation, but also close adverse events management and consideration of social and patient-related factors. Psychological aspects after transplantation should never be neglected and the influence of mental component of quality of life and depressive symptoms on adherence should not be underestimated. Transplant patient care

should gather multi-disciplinary teams, including allied professionals, and include psychological and behavioural interventions, in order to reach the best possible adherence.

Acknowledgements

We thank all the members of the different teams and the contributors who collaborated in the EPIGREN and EPHEGREN studies for their excellent support and all the investigators and patients for their active participation in the study.

We particularly thank Aurélie Desseix and Séverine Ponsard for their precious help in collecting patients' data.

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Table 1. data collected at each scheduled study visit (months post-transplantation) for EPIGREN (x) and EPHEGREN (o).

Collected data	Source/tool	M1	M3	M6	M9	M12	M18	M24	M30	M36
Adherence	PRO/MMAS-4	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Quality of Life	PRO/SF36	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
AE reported by the patient ¹	PRO/AE list	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Socio-demographic data	PRO	x / o								
Immunosuppressants (type/dosage/switch)	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Socio-demographic data	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
AE reported by the medical team	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Rejection (date)	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Return to dialysis	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
infections	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o
Biological data (creatinine...)	Medical record	x / o	x / o	x / o	x	x / o	x / o	x / o	x	x / o

¹ dedicated list which included, but was not limited to: malaise, pain, muscle weakness, weight changes, oedema, depression, anxiety, sleep disorder, physical modifications, sexual disorders, diarrhea

Table 2. Characteristics of the patients included in the two cohort studies.

Variable	EPIGREN cohort	EPHEGREN cohort	p
N	345	367	
median follow-up month	12	24	
Age, mean±SD (years)	51.1±13.1	54.5±13.6	<0.001
Gender (M/F)	219/126	240/127	0.64
Education			
University and College n (%)	101 (29.3%)	Not collected	NA
Primary and high school n (%)	223 (64.6%)	Not collected	NA
Unknown n (%)	21 (6.1 %)	Not collected	NA
Occupational status			
Active/other n (%)	141 (40.9%)	141 (38.4%)	0.67
Retired/without professional activity n (%)	180 (52.2%)	214 (58.3%)	0.22
Unknown n (%)	24 (6.9 %)	12 (3.3%)	0.67
Living arrangement			
Partner n (%)	242 (70.1%)	Not collected	NA
Single n (%)	74 (21.5%)	Not collected	NA
Unknown n (%)	29 (8.4%)	Not collected	NA
Kidney transplantation order			
1	314 (91.0%)	319 (86.9%)	0.10
>1	31 (9.0%)	48 (13.1%)	0.56
Number of patients with rejection within the follow-up period	46 (13.3%)	46 (12.5%)	0.90
Number of patients who were put back on dialysis	4 (1.2%)	13 (3.5%)	0.81
Number of study visits			
≥4	310	358	
≥6	223	283	
≥8	100	115	
≥9	48	5	

Table 3. MMAS-4 scores at each scheduled study visit (months post-transplantation).

		M1	M3	M6	M9	M12	M18	M24	M30	M36
EPIGREN	Questionnaires collected (n)	324	302	266	238	232	107	112	45	43
	Adherent patients (n, %)	302 (93.2)	267 (88.4)	220 (82.7)	199 (83.6)	187 (80.6)	81 (75.7)	89 (79.5)	30 (66.7)	34 (79.1)
EPHEGREN	Questionnaires collected (n)	353	335	311	NA	269	195	183	NA	133
	Adherent patients (n, %)	336 (95.2)	312 (93.1)	277 (89.1)	NA	250 (92.9)	183 (93.8)	159 (86.9)	NA	114 (85.7)

Table 4. Characteristics of the latent class model developed using the 24-month follow-up data / *validated using the 36-month follow-up data* (EPIGREN cohort only).

	Class1: non-adherent patients		Class2: adherent patients	
	24-month follow-up data	36-month follow-up data	24-month follow-up data	36-month follow-up data
N	52	48	293	297
%	15	14	85	86
Mean of posterior probabilities	0.97	0.97	0.98	0.98
Intercept ^a	0.000 ± 0.000	0.000 ± 0.000	-1.301 ± 0.128	-1.625 ± 0.140
Slope ^a	0.124 ± 0.012	0.085 ± 0.012	0.009 ± 0.004	0.012 ± 0.005

^aParameters in the latent process scale after transformation of MMAS-4 scores

Table 5. Statistical comparisons between the 2 adherence classes (EPIGREN cohort).

	Class1: non-adherent patients	Class2: adherent patients	p
	N = 52	N = 293	
Follow-up duration (years)	9.1±8.5	9.2±8.3	0.932
Age (years)	44±14	52±13	<0.001
MMAS-4 score at 1 month	0.47±0.67	0.02±0.14	<0.001
Professional activity (yes)	25%	9%	0.014
SF36 MCS at one month	41±13	47±11	0.015
SF36 PCS at one month	41±8	40±9	NS
Depression reported by patient	13%	5%	0.001
High study level (yes)	37%	15%	NS
Infection episodes (y vs. n)	55.8%	55.3%	NS
Rejection episodes (y vs. n)	9.6%	13.7%	NS
CMV Infection episodes (y vs. n)	7.7%	18.4%	NS
Diarrhea episodes (y vs. n)	59.6%	51.2%	NS
Rejection episodes (y vs. n)	9.6%	13.6%	NS
Return to dialysis (y vs. n)	1.9%	3.7%	NS
Death	1.9%	3.1%	NS
Serum creatinine, µmol/l	132 ± 32	144 ± 78	NS
Number of non-adherence reports			
0	0 (0%)	228 (78%)	
1 - 2	20 (38%)	63 (22%)	
>=3	32 (62%)	2 (1%)	

Table 6. Intra-patient variability of exposure to immunosuppressive drugs (calcineurin inhibitors).

IS trough concentration	Population	Mean (μ/l)	Min (μ/l)	Max (μ/l)	Median (μ/l)	SD (μ/l)	Coefficient of variation (%)	Sample size (n)
Tacrolimus	Global population	9.2	1	58	8.6	4.48	48.5	5772
	Class 1	9.1	1	37.8	8.7	3.9	42.8	972
	Class 2	9.3	2	58	8.5	4.6	49.5	4800
Ciclosporin	Global population	165.5	21	496	147	85.8	51.8	1139
	Class 1	157.3	21	493	140	83.2	52.9	237
	Class 2	167.6	26	496	148	86.4	51.6	902

Figure legends

Figure 1: Flow of participants for the two cohorts.

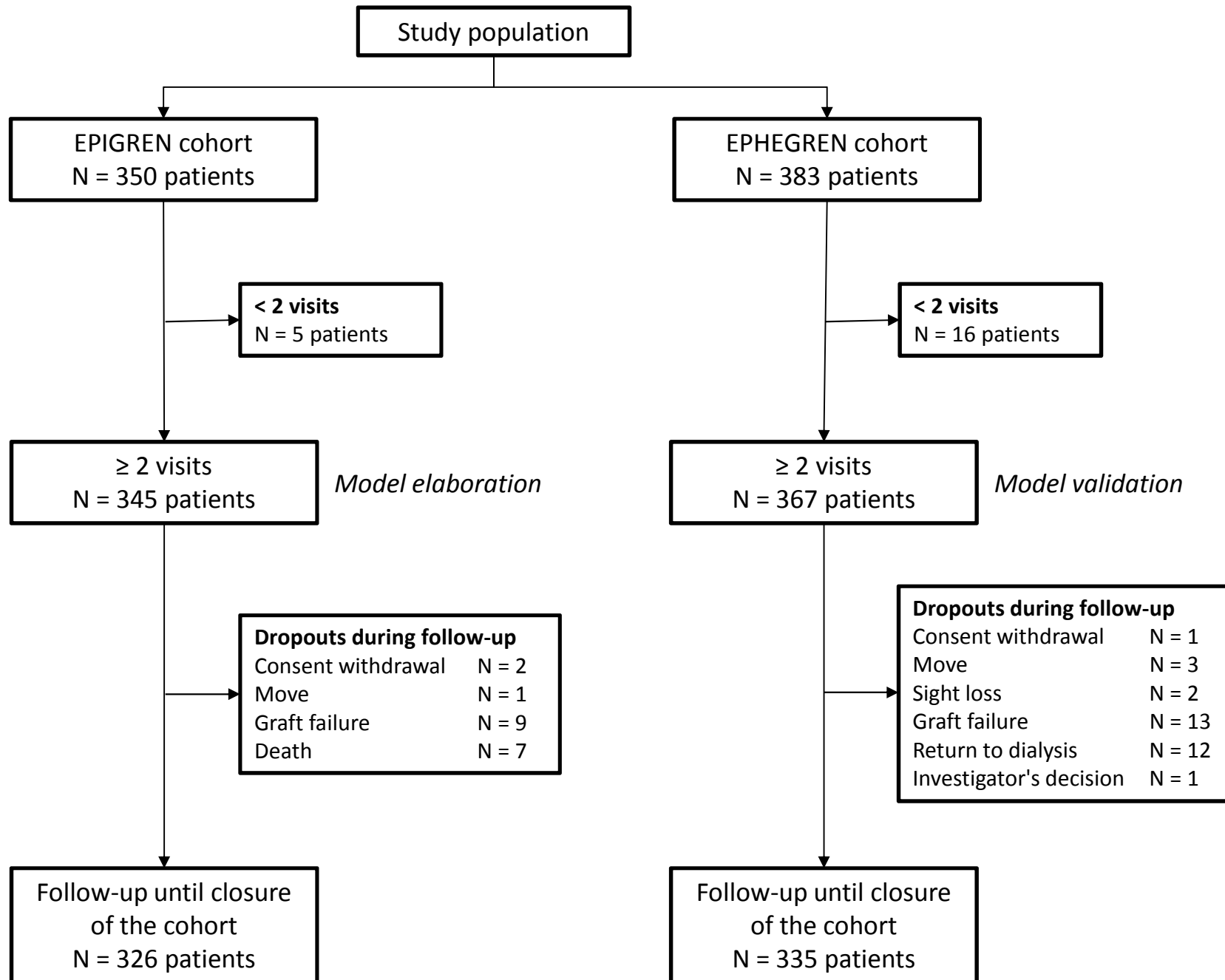
Figure 2: Class-specific mean adherence predicted trajectories over time revealed by latent class analysis of the MMAS-4 scale.

Class 1 (red): non-adherent patients; Class 2 (black): adherent patients.

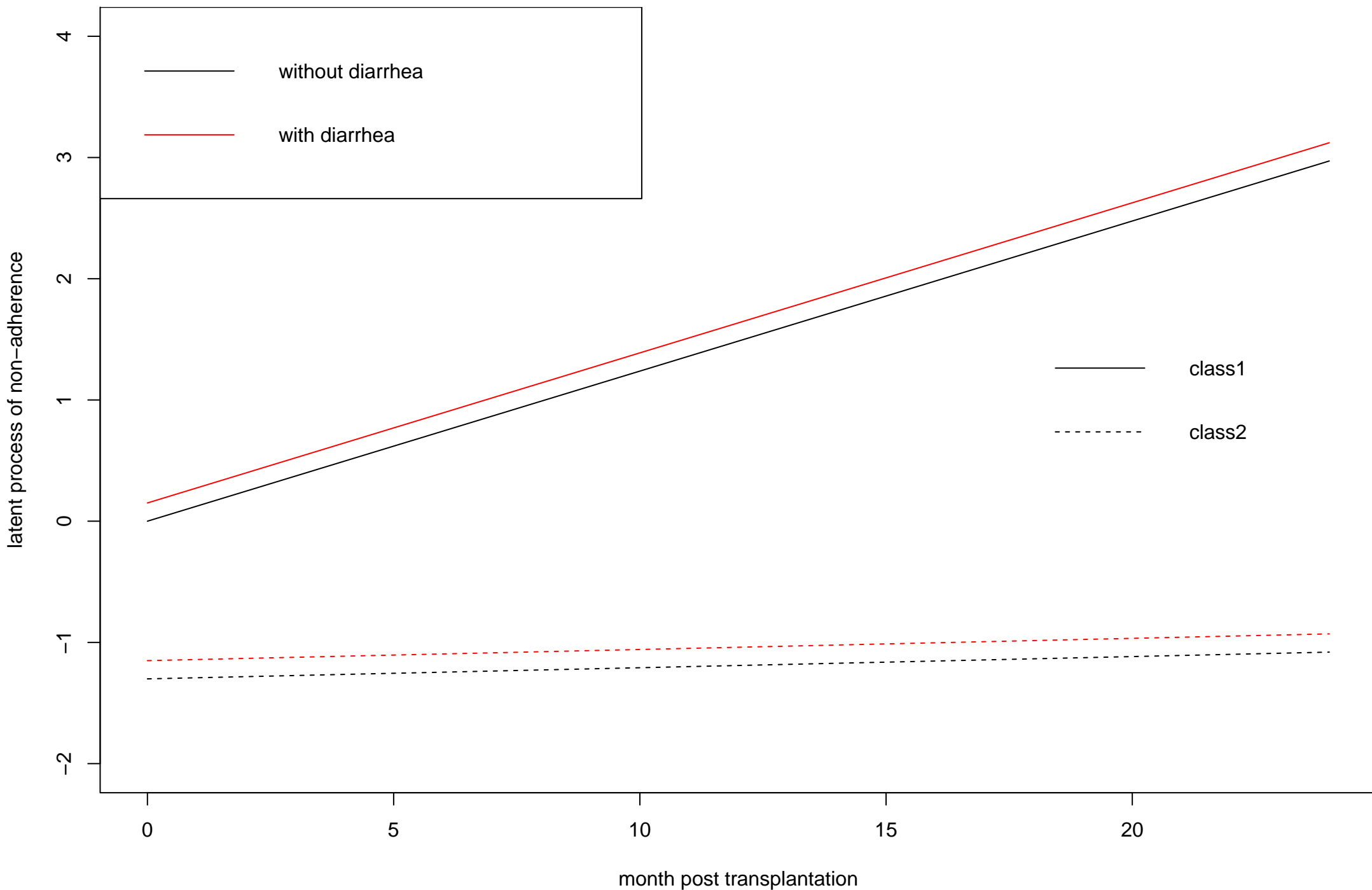
Figure 3: Goodness-of-fit of the model developed using 24-month follow-up data of the EPIGREN (development) cohort: weighted observations and weighted mean of subject-specific predictions of the model with 2 latent classes. This plot provides the comparison between observed and predicted longitudinal data with subject-specific predictions. (Class 1: non-adherent patients; Class 2: adherent patients).

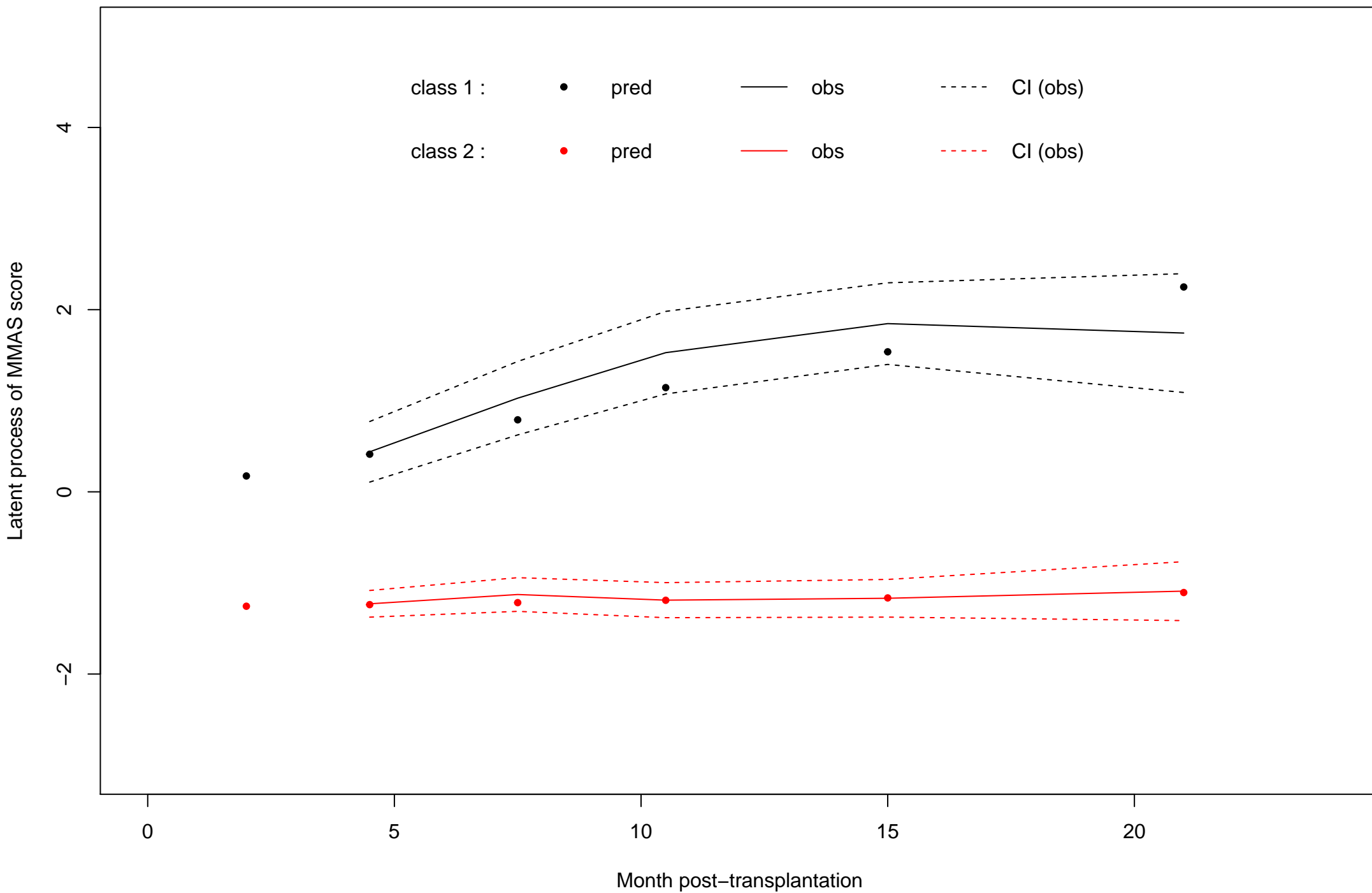
Figure 4: Goodness-of-fit of the model developed using 24-month follow-up data of the EPHEGREN (validation) cohort: weighted observations and weighted mean of subject-specific predictions of the model with 2 latent classes. This plot provides the comparison between observed and predicted longitudinal data with subject-specific predictions (Class 1: non-adherent patients; Class 2: adherent patients).

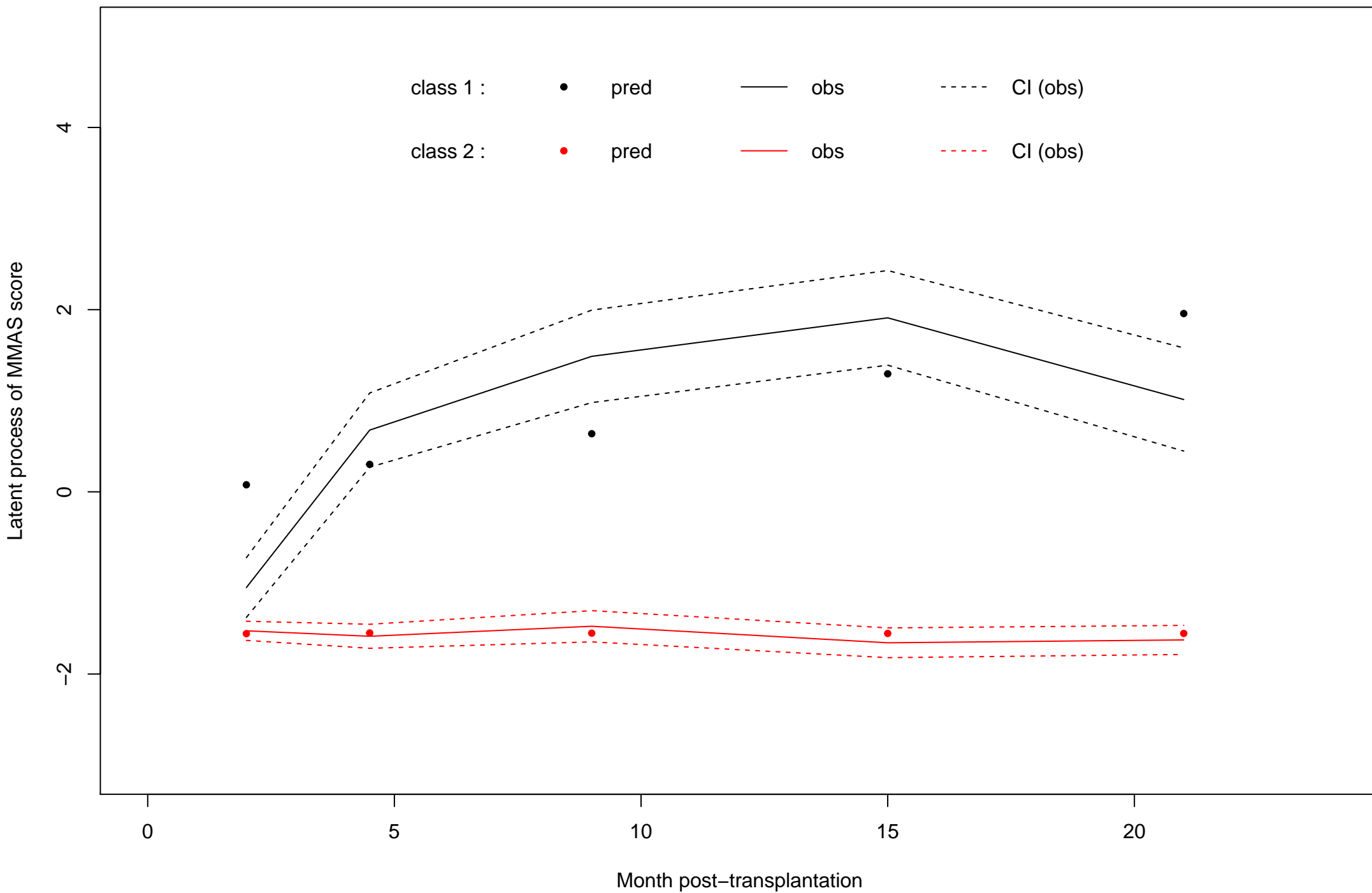
Figure 5: Kaplan–Meier curves of rejection-free survival in non-adherent (Class 1) or adherent (Class 2) patients.



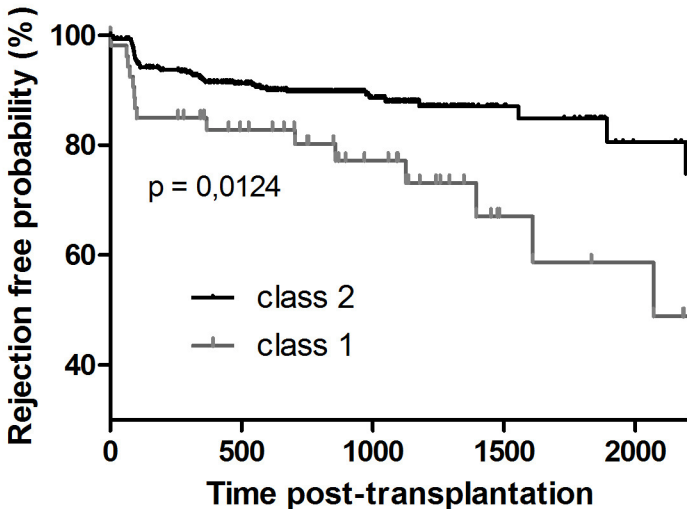
Class-specific mean predicted trajectory







Rejection-free survival



time (days)	0	500	1000	1500	2000
class 2	449	337	148	42	16
class 1	54	37	22	8	6