Hemoglobin Evolution In Hemodialysis Patients

Longitudinal Data Analysis Project 1

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Study objectives

To investigate:

- The evolution of hemoglobin (Hgb) over time in hemodialysis patients
- How this evolution is influenced by EPO dose, iron deficiency status, age, and sex

Methods

Dataset

- Longitudinal data of 3823 hemodialysis patients over six months:
  - Monthly Hgb concentrations
  - Monthly Erythropoietin (EPO): EPO for the next month was decided by the Hgb level of the current month
  - Iron deficiency status at each month
  - Background data: age and sex
- Unbalanced data: not all patients were follow the whole six months

Methods

Exploratory Data Analyses

- Individual-specific profiles
- Graphical methods to explore mean structure, variance structure and correlation structure
- Test linear and quadratic relationship of each patient' Hgb levels and time: R^2_{meta}

Summary statistics

- Analysis of each time point: comparison about hemoglobin levels between female and male group at each time point
- Analysis of increment: subject-specific changes of hemoglobin from baseline (y_{i1}) to the last observation (y_{in_i}): $y_{in_i} - y_{i1}$
- Area under the curve:

$$AUC_i = (t_{i2} - t_{i1})X(y_{i1} + y_{i2})/2 + (t_{i3} - t_{i2})X(y_{i2} + y_{i3})/2 + ...$$

Methods

Multivariate model

- Initial model, with unstructured covariance:

$$
\begin{aligned}
Y_{ij} = {} & \beta_0 + \beta_1 \,\text{age}_i + \beta_2 \,\text{sex}_i + \beta_3 \,\text{iron}_{ij} + \beta_4 \,\text{dose}_{ij} + \beta_5 \,\text{month}_j + \beta_6 \,\text{month}_j^2 \\
& + \beta_7(\text{dose}_{ij} \times \text{age}_i) + \beta_8(\text{dose}_{ij} \times \text{sex}_i) + \beta_9(\text{dose}_{ij} \times \text{iron}_{ij}) + \beta_{10}(\text{dose}_{ij} \times \text{month}_j) \\
& + \beta_{11}(\text{month}_j \times \text{age}_i) + \beta_{12}(\text{month}_j \times \text{sex}_i) + \beta_{13}(\text{month}_j \times \text{iron}_{ij}) + \epsilon_{ij}
\end{aligned}
\tag{1}
$$

- Reduce mean structure: F-test
- Compare different covariance structures using LR test: unstructured type, simple type, compound symmetry type, banded type, first-order autoregressive type and Toeplitz type

Methods

Two-stage analysis model

Stage 1: Linear regression model for each subject separately

Linear effect of time Hgb levels:

$$Y_{ij} = \beta_{1i} + \beta_{2i} t_{ij} + \epsilon_{ij}, \quad j = 0, \dots, 5$$

Stage 2: Explain variability in the subject-specific regression coefficients using known covariates

$$\begin{aligned} \beta_{1i} &= \beta_0^{(1)} + \beta_{\text{Age}}^{(1)} \cdot \text{Age}_i + b_{1i} \\ \beta_{2i} &= \beta_0^{(2)} + \beta_{\text{Age}}^{(2)} \cdot \text{Age}_i + b_{2i} \end{aligned} \tag{2}$$

- b_{1i}, b_{2i} are independent and $\sim N(0, D)$

Methods

Linear mixed model

Four-stage model building process:

Step 1: elaborated LMM

$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_3 Dose_{ij} + \beta_4 Iron_{ij} + \beta_5 t_{ij} + \\ (\beta_6 Age_i + \beta_7 Sex_i + \beta_7 Dose_{ij} + \beta_8 Iron_{ij}) t_{ij} + (\beta_9 Age_i + \beta_{10} Sex_i + \beta_{11} Iron_{ij}) Dose_{ij} + \\ b_{1i} + b_{2j} t_{ij} + \epsilon_{ij} \tag{3}$$

Methods

Step 2: Test serial correlation function in residual covariance structure using REML log-likelihood

Step 3: Reduce random effect structure using Likelihood ratio test

Step 4: Reduce mean structure using F-test

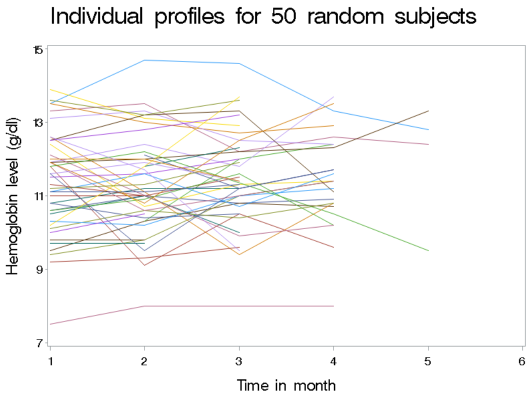
- Compare model from step 3 with models removing interaction effects one by one, using F-test

Results

Exploratory Data Analysis

- Individual profiles

There exists both within-subject and between-subject variability in Hgb levels over time

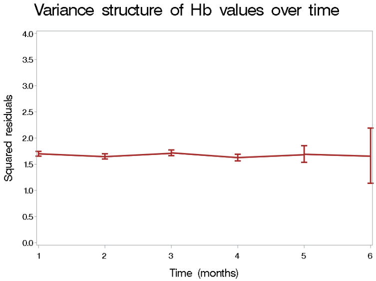


Results

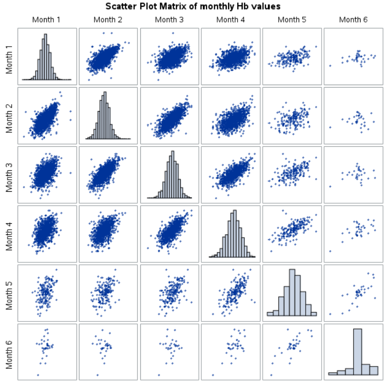
Exploratory Data Analysis

- Mean structure

- Variance structure



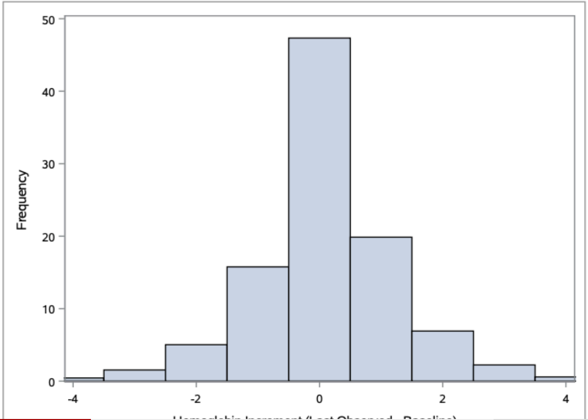
- Covariance structure



Results

Summary statistics

- Analysis of increments:



Multivariate model

Finding parsimonous mean structure

- Reduce each term and perform F-test against the full model:

Reduction	DF	F-value	Pr > F
$month^2$	1	1.14	0.28
*dose*sex*, *dose*age* and *dose*iron*	3	1.63	0.18
*month*age and month*sex*	5	1.95	0.08
*month*iron*	6	2.71	0.01
*month*dose*	6	6.73	<0.001

Multivariate model

Finding appropriate covariance structure

Covariance structure	Prameters	-2 Log Likelihood	G^2	df	p-value
Unstructured	21	27693.1			
Simple	1	32007.9	4314.8	20	$<$0.001
Compound symmetry	2	28358.7	665.6	19	$<$0.001
Banded	21	28948.1	1255.0	0	$<$0.001
First-order autoregressive	2	27755.5	62.4	19	$<$0.001
Toeplitz	6	27735.8	42.7	15	0.002

Multivariate model

Final model: unstructured covariance structure

- Effect estimates:

Effect	Estimate	Standard Error	p-value
Intercept	10.61	0.09	$<$0.001
Age	0.003	0.001	0.03
Male	0.10	0.04	0.008
Iron deficiency	0.17	0.03	$<$0.001
EPO dose	0.0005	0.001	0.006
Month	-0.04	0.01	0.01
Dose*month	0.0005	0.0001	$<$0.001
Iron deficiency*month	-0.05	0.02	0.01

Two-stage analysis

Stage-1 analysis

- Subject-specific linear regression model for patients with at least 2 measurements

Variable	N	Mean	Std Dev	Minimum	Maximum
Intercept	2933	10.92	1.36	4.45	18.77
month	2933	0.03	0.69	-5.00	7.10

Two-stage analysis

Stage-2 analysis

- Effect of age on the intercept:

Variable	Parameter Estimate	Standard Error	T Value	P-value
Intercept	10.61	0.108	98.53	<0.0001
AGE	0.005	0.002	2.97	0.003

Two-stage analysis

Stage-2 analysis

- Effect of age on the slope:

Variable	Parameter Estimate	Standard Error	T Value	P-value
Intercept	0.157	0.0553	2.83	0.005
AGE	-0.002	0.0009	-2.17	0.030

Linear mixed model

Mean structure was identical to the multivariate model

Effect	LMM Estimate (SE)	P-value	Multivariate Estimate (SE)	P-value
Intercept	10.62 (0.1)	<0.0001	10.61 (0.1)	<0.0001
EPO dose	0.0005 (0.0002)	0.005	0.0005 (0.0002)	0.006
Age	0.0027 (0.001)	0.04	0.0028 (0.001)	0.03
Male	0.10 (0.04)	0.01	0.10 (0.04)	0.008
Iron deficiency	0.17 (0.03)	<0.0001	0.17 (0.03)	<0.0001
Month	-0.028 (0.02)	0.07	-0.038 (0.02)	0.02
EPO dose * month	0.0005 (0.0001)	<0.0001	0.0006 (0.0001)	<0.0001
Iron deficiency * month	-0.043 (0.02)	0.02	-0.047 (0.02)	0.01

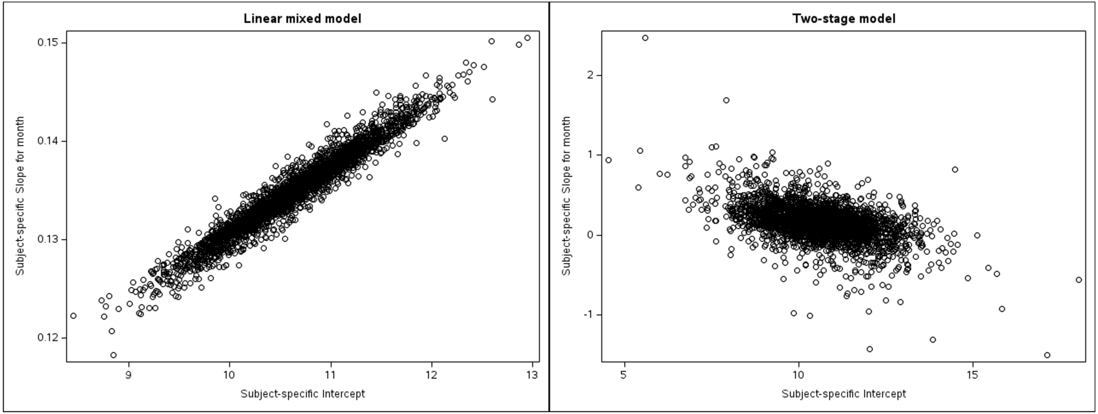
Linear mixed model

Variance components

Effect	Parameter	Estimate (SE)
Covariance of b_i		
var(b_{1i})	d_{11}	0.69 (0.056)
Measurement error variance		
var($\epsilon_{(1)ij}$)	σ^2	0.29 (0.016)
Gaussian serial correlation		
var($\epsilon_{(2)ij}$)	τ^2	1.9 (0.13)

Linear mixed model vs two-stage model

- Random slope against random intercept:



Conclusions

- The mean Hgb concentration decreases over time
- Higher EPO dose »> higher Hgb over time
- Iron-deficient patients »> higher baseline Hgb, Hgb decreases over time
- Higher EPO dose »> higher baseline Hgb
- Older patients and male patients »> higher baseline Hgb
- Linear mixed model vs multivariate model

Thank you for your attention!