RESEARCH ARTICLE

A predictive model for estimating the number of erythrocytapheresis or phlebotomy treatments for patients with naïve hereditary hemochromatosis

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Abstract

Background and Aims: Standard treatment for naïve hereditary hemochromatosis patients consists of phlebotomy or a personalized erythrocytapheresis. Erythrocytapheresis is more efficient, but infrequently used because of perceived costs and specialized equipment being needed. The main aim of our study was to develop a model that predicts the number of initial treatment procedures for both treatment methods. This information may help the clinician to select the optimal treatment modality for the individual patient.

Methods: We analyzed retrospective data of 125 newly diagnosed patients (C282Y homozygous), treated either with phlebotomy (n = 54) or erythrocytapheresis (n = 71) until serum ferritin (SF) reached levels ≤100 μg/L. To estimate the required number of treatment procedures multiple linear regression analysis was used for each treatment method separately.

Results: The linear regression model with the best predictive quality ($R^2 = 0.74$ and 0.73 for erythrocytapheresis and phlebotomy respectively) included initial SF, initial hemoglobin (Hb) level, age, and BMI, where initial SF was independently related to the total number of treatment procedures for both treatment methods. The prediction error expressed in RMSPE and RMSDR was lower for erythrocytapheresis than for phlebotomy (3.8 and 4.1 vs 7.0 and 8.0 respectively).

Conclusions: Although the prediction error of the developed model was relatively large, the model may help the clinician to choose the most optimal treatment method for an individual patient. Generally erythrocytapheresis halves the number of treatment procedures for all patients, where the largest reduction (between 55% and 64%) is reached in patients with an initial Hb level ≥ 9 mmol/L (14.5 g/dL).

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INTRODUCTION

Hereditary hemochromatosis (HH) is one of the most commonly inherited metabolic disorders in Caucasians, characterized by an increased iron absorption that is inappropriate to body iron stores resulting in progressive accumulation of tissue iron, especially in the liver, heart, pancreas, joints, skin and gonads.\(^1\) A meta-analysis found that patients with HH who are homozygous for the p.C282Y HFE-gene variant and who have clinical symptoms, for example, fatigue, characteristic arthropathy involving the second and third metacarpophalangeal joints, cardiac failure symptoms, abdominal complaints, skin pigmentation, impotence and moderately elevated transaminases, have an increased risk of developing liver disease and hepatocellular carcinoma.\(^2\)

The therapy of HH is based on the removal of excess in body iron with serum ferritin (SF) levels being used to monitor the effectiveness of treatment.\(^3,4\) Normalization of SF levels by iron depletions could be of benefit for all patients with HH.\(^5\) A recent systemic review including 24 studies and 6000 patients reports an improvement in fatigue, liver function tests, fibrosis, and overall survival following treatment with iron depletion therapy.\(^6\)

To date, standard treatment involves phlebotomy, which in the initial phase is generally performed on a weekly basis removing 450 to 500 mL whole blood per procedure until SF levels are reduced to the target level. While international guidelines up to 2011 advised to aim for SF levels ≤50 \(\mu\)g/L,\(^7,8\) currently SF levels between 50 and 100 \(\mu\)g/L are targeted.\(^9\) Although phlebotomy is very effective, side effects are common and include fatigue, fainting, pain at the venous access site, hematomas, and anemia. These side effects have been reported by 52% of HH patients during the initial phase of treatment, while 16% of patients considered discontinuing phlebotomy when alternative options would be available.\(^9\)

Erythrocytapheresis, a technique in which an apheresis machine selectively removes erythrocytes while returning leucocytes, platelets and plasma to the patient, forms an appropriate alternative for phlebotomy. With erythrocytapheresis, up to 1000 mL of red blood cells (RBCs) per single procedure can be removed compared to 250 mL RBCs per phlebotomy procedure. The volume of RBCs removed is determined individually, based on a patient’s total blood volume (TBV) and actual hematocrit (Hct).\(^10\) The American Association for Apheresis (ASFA) guidelines recommend the use of erythrocytapheresis as an alternative first-line therapy for HH.\(^11\) Results from two randomized,\(^10,12\) and several non-randomized,\(^13-22\) studies showed that the total number of erythrocytapheresis treatments needed is significantly lower, compared to the total number of phlebotomy treatments. Factors such as the initial hemoglobin/hematocrit level and TBV of the individual patient determine the size of these differences.\(^23\) Application of erythrocytapheresis in daily practice may be hindered by the high costs per single procedure. However, due to a considerable reduction in the total number of treatment procedures needed, erythrocytapheresis was demonstrated to be cost-effective.\(^10\) Accurately predicting the needed number of procedures prior to initiation of treatment, may enable shared decision-making weighing both patient needs and HH treatment effectiveness.

The aim of the present study was to develop a prediction model that accurately estimates the number of procedures needed for the initial treatment of newly diagnosed HH patients, in order to decrease SF value to target levels ≤100 \(\mu\)g/L, using either phlebotomy or erythrocytapheresis. This model could help the clinician to select the optimal treatment modality for the individual patient. Hereby it is important to mention that optimal treatment modality depends on factors such as: the least number of treatment procedures, difference in local costs for both treatment methods, distance to treatment locality with availability of apheresis equipment, preference of the individual patient. A low number of treatment procedures is important for minimizing the occurrence of adverse events such as fatigue and patient needle sticks/discomfort, reducing length of treatment to achieve normal SF value, minimizing costs resulting from the loss of hours absent from work and travel costs.

MATERIALS AND METHODS

2.1 Study participants

Retrospective (2002-2018) data of 125 newly diagnosed patients with HH was analyzed. All patients were homozygous for the p.C282Y HFE-gene variant and were treated by either phlebotomy (n = 54) or erythrocytapheresis (n = 71) until SF ≤100 \(\mu\)g/L was reached. Thirty-eight of these patients (19 treated with phlebotomy and 19 with erythrocytapheresis) participated in an earlier published randomized controlled trial (RCT, ClinicalTrials.gov).
identifier NCT00202436).10 The other 87 patients (35 treated with phlebotomy and 52 treated with erythrocytapheresis) were treated in one of the four medical centers (Zuyderland Medical Center Heerlen, HAGA Teaching Hospital The Hague, Radboud University Medical Center Nijmegen, Leiden University Medical Center Leiden), or at the national Sanquin Blood Bank. The choice for erythrocytapheresis treatment was based only on the presence of apheresis equipment on treatment location. All patients were treated according to Dutch guidelines. It should be mentioned that over time guidelines were adjusted, namely target SF level at the end of depletion phase is changed from ≤50 to 50-100 μg/L.24 Participants of the RCT gave written informed consent for use of all data. Data of all participants was anonymized before being analyzed.

2.2 | Treatments methods

In the phlebotomy group, per single treatment procedure 500 mL whole blood was withdrawn once weekly. In the erythrocytapheresis group, per single treatment procedure 300 to 1000 mL RBCs were withdrawn once every 2 to 4 weeks, depending on the estimated TBV and Hct of the patient. The minimal targeted post-procedure Hct was set at 30%. Erythrocytapheresis procedures were carried out using an erythrocytapheresis collection device 944 and MCS+ equipment (Haemonetics Corporation, Braintree, Massachusetts) or flow automatic centrifugal cell separator Cobe Spectra and cell separator Trima Accel (Terumo BCT, Lakewood, Colorado).

For a full description of both treatments methods we refer to our earlier study.10

2.3 | Monitoring of treatment

In patients who were treated according to the RCT protocol and in all patients treated with erythrocytapheresis, prior to and after each treatment procedure Hb, Hct, mean corpuscular volume (MCV), SF, serum iron (SI), and transferrin saturation (TS) were measured. In all other patients, these measurements were performed on a regular basis.

Hematologic characteristics were assessed using a routine photometry method (XN9000, Sysmex Europe GmbH, Germany). Reference ranges for Hb were 8.2 to 11 mmol/L (13.2-17.7 g/dL) for males and 7.3 to 9.7 mmol/L (11.8-15.6 g/dL) for females. SI was measured by the photometry method (COBAS8000, Roche Diagnostics, F.Hoffman-La Roche Ltd, Basel, Switzerland) with a reference range of 14 to 27 μmol/L for males and 11 to 25 μmol/L for females. SF was measured by a lumincent immunoassay (COBAS 6000, Roche Diagnostics, F. Hoffman-La Roche Ltd, Basel, Switzerland) with a reference range of 30 to 400 μg/L for males and 10 to 200 μg/L for females. TS was calculated from SI concentration and transferrin concentration with the formula:

\[ TS(\%) = \left( \frac{\text{SI}}{25} \right) \times 100\% \]

3 | Statistical analysis

3.1 | Data analysis

Numerical variables were presented by mean (±SD) or median (interquartile range [IQR]), that is, 25th to 75th percentile (P25-P75) and categorical variables by numbers (%). Differences between treatment methods (erythrocytapheresis/phlebotomy) were assessed using an independent-samples t-test for numerical variables, and a chi-square test or Fisher’s exact test, (whenever appropriate) for categorical variables.

To estimate the number of treatment procedures needed during the initial treatment of HH, thereby aiming for target SF levels ≤100 μg/L, multiple linear regression analysis with all predictors (initial SF, initial Hb count, age, and TBV) in the model (Model A) was performed for each treatment method separately. Two sensitivity analyses with TBV being replaced by either body mass index (BMI) (Model B) or body weight (Model C) were additionally performed. Further, we assessed whether female sex and participation in the RCT influenced the number of treatment procedures.

Overall prediction quality of the model was expressed in R-square (closer to 1 is better fit to the data) as well as in (square) root of the mean squared prediction error (RMSPE; closer to 0 is better). In addition, the (square) root of the mean squared deleted residuals (RMSDR; closer to 0 is better) were computed, which is an internally validated measure of the overall prediction quality of the model, as the predicted value for a patient was based on a model which was estimated using all patients except that particular patient.

The estimated number of treatment procedures was also translated to treatment duration, where treatment interval (time between two treatments) for phlebotomy was set at 10 days for initial Hb 8 mmol/L, (12.9 g/dL) and 7 days for initial Hb 9 and 10 mmol/L, (14.5 and 16.1 g/dL) for erythrocytapheresis 21 days for Hb 8 mmol/L, (12.9 g/dL) and 14 days for Hb 9 and 10 mmol/L (14.5 and 16.1 g/dL). The treatment intervals were based on the mean intervals observed in a previous study,10 and the experience with the treatment of patients with phlebotomy and erythrocytapheresis.

A P-value ≤0.05 was considered statistically significant. All analyses were performed using computer software (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, New York).
**TABLE 1**  Baseline and end of treatment characteristics of both treatment groups

| Parameter/Method               | Erythrocytapheresis (n = 71) | Phlebotomy (n = 54) | P value |
|-------------------------------|------------------------------|--------------------|---------|
| Age (years)                   | 55 (12)                     | 53 (12)            | .367    |
| Male (N (%))                  | 51 (71.8)                   | 44 (81.5)          | .211    |
| Height (cm)                   | 174 (11)                    | 177 (9)            | .130    |
| Weight (kg)                   | 82 (15)                     | 84 (15)            | .373    |
| BMI                           | 26.8 (3.8)                  | 26.9 (4.7)         | .922    |
| Estimated TBV (mL)            | 5063 (894)                  | 5301 (762)         | .121    |
| Initial serum ferritin        | 1174 (785-1961)             | 1174 (716-1809)    | .725d   |
| Final serum ferritin          | 81 (68-90)                  | 86 (73-95)         | .194d   |
| Initial hemoglobin (mmol/L)   | 9.3 (0.7)                   | 9.6 (0.8)          | .014    |
| Final hemoglobin (mmol/L)     | 14.9 (0.7)                  | 15.5 (0.8)         | .014    |
| Number of treatment procedures| 11 (8)                      | 22 (13)            | <.001   |

**Note:** Presented data are means (SD), unless otherwise stated. Reference ranges: serum ferritin: 30 to 400 μg/L (males) and 10 to 200 μg/L (females); hemoglobin: 8.2 to 11.0 mmol/L (males) and 7.3-9.7 mmol/L (females), 1 mmol/L = 1.61 g/dL, 1 g/dL = 0.6206 mmol/L. Abbreviation: IQR, interquartile range.

aMedian (IQR).
b1 missing value.
c3 missing value.
dMann-Whitney test.

**TABLE 2**  Linear regression models for predicting number of treatment procedures for erythrocytapheresis and phlebotomy

| Variable               | Erythrocytapheresis (n = 71) | Phlebotomy (n = 53) |
|------------------------|------------------------------|--------------------|
| **Model A**            |                              |                    |
| Constant               | 16.744 (1.572, 31.915)       | 12.715 (−20.186, 45.616) |
| Initial SF             | 0.005 (0.004, 0.005)         | 0.011 (0.008, 0.013) |
| Initial Hb             | −1.698 (−3.184, −0.211)      | −1.115 (−4.075, 1.845) |
| TBV                    | −0.0001 (−0.001, 0.001)      | −0.001 (−0.004, 0.002) |
| Age                    | 0.060 (−0.030, 0.149)        | 0.148 (−0.048, 0.343) |

| Variable               | Erythrocytapheresis (n = 71) | Phlebotomy (n = 53) |
|------------------------|------------------------------|--------------------|
| **Model B**            |                              |                    |
| Constant               | 18.583 (3.655, 33.512)       | 19.795 (−10.310, 49.899) |
| Initial SF             | 0.005 (0.004, 0.005)         | 0.011 (0.009, 0.013) |
| Initial Hb             | −1.465 (−2.882, −0.048)      | −0.686 (−3.420, 2.049) |
| BMI                    | −0.195 (−0.458, 0.068)       | −0.551 (−0.996, −0.105) |
| Age                    | 0.075 (−0.010, 0.160)        | 0.160 (−0.018, 0.338) |

| Variable               | Erythrocytapheresis (n = 71) | Phlebotomy (n = 53) |
|------------------------|------------------------------|--------------------|
| **Model C**            |                              |                    |
| Constant               | 17.316 (2.385, 32.248)       | 16.851 (−14.353, 48.055) |
| Initial SF             | 0.005 (0.004, 0.005)         | 0.011 (0.009, 0.013) |
| Initial Hb             | −1.528 (−2.993, −0.063)      | −0.770 (−3.627, 2.087) |
| Body weight            | −0.030 (−0.099, 0.039)       | −0.119 (−0.269, 0.031) |
| Age                    | 0.056 (−0.029, 0.141)        | 0.136 (−0.050, 0.322) |

Abbreviations: BMI, body mass index; Hb, hemoglobin; SF, serum ferritin; TBV, total blood volume.

aOne patient was excluded from analyses due to missing data (weight, height, BMI, TBV).
bB = unstandardized coefficient, which represents the difference in mean outcome if the variable increases with one unit (eg, 1 μg/L increase for initial SF).
cMissing data by 1 patient.
4 | RESULTS

4.1 | Patient characteristics

Baseline patient characteristics are summarized in Table 1. Both groups were comparable, with exception of a significantly lower initial mean Hb value in patients in the erythrocytapheresis group. The mean observed number of treatment procedures needed to reach a targeted SF value ≤100 μg/L was significantly lower in patients treated with erythrocytapheresis (11 ± 8) than in the phlebotomy group (22 ± 13; P < .001; Table 1).

4.2 | Number of estimated treatment procedures

Three linear regression models with different predictors (Model A: initial SF, initial Hb count, age, and TBV, Model B: same model as A, but with BMI instead of TBV, and Model C: same as model A, but with body weight instead of TBV) were used separately for each treatment method (Table 2). Since female sex and participation in the RCT did not contribute significantly to the models (P = .892 and .713 for sex, P = .488 and .334 for participation in the RCT, respectively), these variables were not included in the final models. Initial SF value was the only predictor independently related to the total number of treatment procedures for both treatment methods in all three models (P < .001), while initial Hb value was only significant for erythrocytapheresis in all three models (P-value = .026, .043, and .041) and BMI value for phlebotomy (P = .016).

For both treatment methods, model B (including initial SF, initial Hb level, age, and BMI) showed the highest predictive quality (R² = 0.74, for erythrocytapheresis; R² = 0.73, for phlebotomy) and was used to establish corresponding prediction formulas presented in Table 3.

The prediction error expressed in RMSPE and RMSDR was lower for erythrocytapheresis than for phlebotomy (3.8 and 4.1 vs 7.0 and 8.0, respectively), which was also reflected by plotting the predicted number of treatment procedures (based on model B) against the observed numbers.

### TABLE 3 Prediction rule for estimated number of treatment procedures for erythrocytapheresis method (R² = 0.74; RMSPE = 3.8; RMSD = 4.1) and phlebotomy method (R² = 0.73, RMSPE = 7.0; RMSD = 8.0)

- **Erythrocytapheresis**
  - \( X_e = 18.6 + 0.005 \times \text{initial SF} - 1.5 \times \text{initial Hb} - 0.19 \times \text{BMI} + 0.07 \times \text{age} \)

- **Phlebotomy**
  - \( X_p = 19.8 + 0.011 \times \text{initial SF} - 0.7 \times \text{initial Hb} - 0.55 \times \text{BMI} + 0.16 \times \text{age} \)

**Note:** In case Hb is expressed in g/dL, please convert it to mmol/L (1 g/dL = 0.6206 mmol/L); for example 15 g/dL = 15*0.6206 = 9.309 mmol/L, so Hb = 9.309 should then be entered in the formula.

### FIGURE 1

A. Observed versus predicted number of treatment procedures using erythrocytapheresis as treatment modality. Predicted numbers are based on model B, using initial SF, initial Hb count, age and BMI as predictors. \( R^2 = 0.74; \) RMSPE = 3.8; RMSD = 4.1. The line is presented, where points on this line imply that the predicted and observed numbers were the same.

B. Observed vs predicted number of treatment procedures using phlebotomy as treatment modality. Predicted numbers are based on model B, using initial SF, initial Hb count, age and BMI as predictors \( R^2 = 0.73; \) RMSPE = 7.0; RMSD = 8.0. The line is presented, where points on this line imply that the predicted and observed numbers were the same.
number of treatment procedures for erythrocytapheresis (Figure 1A) and phlebotomy (Figure 1B).

Estimated numbers of treatment procedures calculated according to the established models are presented in Table 4. As expected, the number of treatment procedures is positively associated with increasing levels of initial SF for both treatment methods and negatively associated with higher values of BMI. In general, erythrocytapheresis halves the number of procedures needed to achieve target levels in all patients. The largest reduction in number of needed treatments, (between 55% and 64%; ratio 2.2-2.8) is reached for patients with a high initial Hb level (≥ 9 mmol/L (14.5 g/dL) (Table 4). For this group of patients, erythrocytapheresis also reduces treatment duration between 11% and 33% as shown in Table 4.

**Table 4** Estimated number of treatment procedures and treatment duration in days for erythrocytapheresis (E) and phlebotomy (P) based on the regression models in Table 2, where values for initial SF (=1000, 2000, 3000 μg/L), initial Hb (=8.0, 9.0, 10.0 mmol/L = 12.9, 14.5, 16.1 g/dL), BMI (=20, 26, 32), and age (=55 years) were chosen based on data (within the observed range). Reduction (%) in number of treatments and treatment duration is computed in terms of number of procedures required for phlebotomy, that is, 100%*(P − E)/P.

| Input parameters | Number of estimated treatments | Reduction in number of treatments | Estimated treatment duration (days) | Reduction in treatment duration |
|------------------|-------------------------------|----------------------------------|-----------------------------------|-----------------------------|
| **SF (μg/L)**    | **Hb (mmol/L)/**              | **BMI** | **E** | **P** | **%** | **E** | **P** | **%** |
| 1000             | 8/12.9                        | 20     | 11   | 23   | 2.1  | 52.2 | 210  | 220  | 4.5  |
| 1000             | 8/12.9                        | 26     | 10   | 20   | 2.0  | 50.0 | 189  | 190  | 0.5  |
| 1000             | 8/12.9                        | 32     | 9    | 16   | 1.8  | 43.8 | 168  | 150  | −12.0 |
| 1000             | 9/14.5                        | 20     | 10   | 22   | 2.2  | 54.5 | 126  | 147  | 14.3 |
| 1000             | 9/14.5                        | 26     | 8    | 19   | 2.4  | 57.9 | 98   | 126  | 22.2 |
| 1000             | 9/14.5                        | 32     | 7    | 16   | 2.3  | 56.3 | 84   | 105  | 20.0 |
| 1000             | 10/16.1                       | 20     | 8    | 22   | 2.8  | 63.6 | 98   | 147  | 33.3 |
| 1000             | 10/16.1                       | 26     | 7    | 18   | 2.6  | 61.1 | 84   | 119  | 29.4 |
| 1000             | 10/16.1                       | 32     | 6    | 15   | 2.5  | 60.0 | 70   | 98   | 28.6 |
| 2000             | 8/12.9                        | 20     | 16   | 34   | 2.1  | 52.9 | 315  | 330  | 4.5  |
| 2000             | 8/12.9                        | 26     | 15   | 31   | 2.1  | 51.6 | 294  | 300  | 2.0  |
| 2000             | 8/12.9                        | 32     | 14   | 27   | 1.9  | 48.1 | 273  | 260  | −5.0 |
| 2000             | 9/14.5                        | 20     | 15   | 33   | 2.2  | 54.5 | 196  | 224  | 12.5 |
| 2000             | 9/14.5                        | 26     | 13   | 30   | 2.3  | 56.7 | 168  | 203  | 17.2 |
| 2000             | 9/14.5                        | 32     | 12   | 27   | 2.3  | 55.6 | 154  | 182  | 15.4 |
| 2000             | 10/16.1                       | 20     | 13   | 33   | 2.5  | 60.6 | 168  | 224  | 25.0 |
| 2000             | 10/16.1                       | 26     | 12   | 29   | 2.4  | 58.6 | 154  | 196  | 21.4 |
| 2000             | 10/16.1                       | 32     | 11   | 26   | 2.4  | 57.7 | 140  | 175  | 20.0 |
| 3000             | 8/12.9                        | 20     | 21   | 45   | 2.1  | 53.3 | 420  | 440  | 4.5  |
| 3000             | 8/12.9                        | 26     | 19   | 38   | 2.0  | 50.0 | 378  | 370  | −2.2 |
| 3000             | 8/12.9                        | 32     | 19   | 38   | 2.0  | 50.0 | 378  | 370  | −2.2 |
| 3000             | 9/14.5                        | 20     | 20   | 44   | 2.2  | 54.5 | 266  | 301  | 11.6 |
| 3000             | 9/14.5                        | 26     | 18   | 41   | 2.3  | 56.1 | 238  | 280  | 15.0 |
| 3000             | 9/14.5                        | 32     | 17   | 38   | 2.2  | 55.3 | 224  | 259  | 13.5 |
| 3000             | 10/16.1                       | 20     | 18   | 44   | 2.4  | 59.1 | 238  | 301  | 20.9 |
| 3000             | 10/16.1                       | 26     | 17   | 40   | 2.4  | 57.5 | 224  | 273  | 17.9 |
| 3000             | 10/16.1                       | 32     | 16   | 37   | 2.3  | 56.8 | 210  | 252  | 16.7 |

Note: Italic values: Ratio P/E treatments = <2 (first choice phlebotomy); bold values: Ratio P/E treatments = 2-2.1 (first choice both); underline values: Ratio P/E treatments = ≥2.1 (first choice erythrocytapheresis.

*A negative reduction indicates that the estimated treatment duration was not beneficial for erythrocytapheresis compared to phlebotomy.

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5 | DISCUSSION

Prior to treatment initiation in an individual HH patient, a reliable estimation of the numbers of procedures needed to reach target SF levels may support an efficient and cost-effective choice of treatment methodology as well as patient contentment and treatment compliance. We developed a prediction model estimating the number of treatment procedures necessary to reduce SF levels ≤100 μg/L, using either phlebotomy or erythrocytapheresis. Although the prediction error was relatively large (internally validated prediction error, in terms of root mean squared deleted residual [RMSDR], was about 4 for erythrocytapheresis and 8 for phlebotomy), erythrocytapheresis generally required only a half of the treatment procedures in comparison to phlebotomy. For patients with a high initial Hb (≥9 mmol/L or = 14.5 g/dL), the reduction was even more than 50%, ranging from 55% to 64% for all values of initial SF, BMI, and age, that were chosen based on the data. These results were in line with those from Evers and colleagues, who also showed the importance of initial Hct value for the efficiency rate of a single erythrocytapheresis procedure compared to a single phlebotomy procedure.

We used two comparable groups of patients, with exception of a significantly lower mean initial Hb level in patients in the erythrocytapheresis group. We have no explanation for this difference, the choice for erythrocytapheresis treatment was based only on a presence of apheresis equipment on treatment location (HAGA Teaching Hospital and Sanquin Blood Bank).

Initial SF was, as expected, a significant predictor for the number of required treatment procedures for both treatment methods. The same was observed by Panch et al., in patients with secondary iron overload and treated with phlebotomy and by Verhaegh et al., in hereditary hemochromatosis patients by predicting the number of phlebotomy treatments needed per year, during the maintenance treatment.

One of the most frequently mentioned obstacles for the use of erythrocytapheresis in daily practice, are costs per single procedure. Concerning the Dutch situation, the costs per single procedure are 3.5 higher compared to a single phlebotomy procedure. However, due to a considerable reduction in the total number of procedures needed to reach the target level of SF the total treatment costs are comparable for both methods.10 The costs from the number of hours absent at work are considerably lower using erythrocytapheresis.10 In addition erythrocytapheresis is the method of preference for the majority of patients.27

Some important limitations have to be considered with regard to this study. First, although internally validated measures of model fit (root mean square deleted residuals) were computed, the sample size within each center was too small to use data from one center for model development and use data from another center(s) for external validation. Therefore, our findings need to be validated in a separate cohort. Second, several additional factors, such as individual clinical patient conditions (liver fibrosis and cirrhosis) and iron reabsorption index (IRI), will have influenced the rate of individual iron mobilization, and thus the accuracy of both models in an individual patient.28,29

6 | CONCLUSION

We developed a model that predicts the number of procedures needed for the initial treatment of newly diagnosed HH patients, in order to decrease SF value to target levels ≤100 μg/L, using either phlebotomy or erythrocytapheresis. Although the prediction error of the developed model was relatively large, the model provides important information about the potential number of required treatments, which is one critical piece of information that can enable a physician to make an informed decision about the optimal treatment modality for the individual patient. We found, in general, that the estimated number of treatment procedures to obtain a SF level ≤ 100 μg/L was about 50% lower for erythrocytapheresis compared to phlebotomy, which even declined more (up to 64%) for patients with a high initial Hb value (≥9 mmol/L or 14.5 g/dL). For this particular group of patients the duration of treatment using erythrocytapheresis was reduced with 11% to 33%. It is important to notice that these prediction models used for estimating number of treatment procedures in an individual HH patient, should be externally validated before these models can be used in daily clinical practice.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest relevant to the manuscript submitted to Journal of Clinical Apheresis.

DATA AVAILABILITY STATEMENT
The Data are available on request from the corresponding author. The data are not publicly available due to privacy/ethical restrictions.

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