An international observational study suggests that artificial intelligence for clinical decision support optimizes anemia management in hemodialysis patients

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Managing anemia in hemodialysis patients can be challenging because of competing therapeutic targets and individual variability. Because therapy recommendations provided by a decision support system can benefit both patients and doctors, we evaluated the impact of an artificial intelligence decision support system, the Anemia Control Model (ACM), on anemia outcomes. Based on patient profiles, the ACM was built to recommend suitable erythropoietic-stimulating agent doses. Our retrospective study consisted of a 12-month control phase (standard anemia care), followed by a 12-month observation phase (ACM-guided care) encompassing 752 patients undergoing hemodialysis therapy in 3 NephroCare clinics located in separate countries. The percentage of hemoglobin values on target, the median darbepoetin dose, and individual hemoglobin fluctuation (estimated from the intrapatient hemoglobin standard deviation) were deemed primary outcomes. In the observation phase, median darbepoetin consumption significantly decreased from 0.63 to 0.46 μg/kg/month, whereas on-target hemoglobin values significantly increased from 70.6% to 76.6%, reaching 83.2% when the ACM suggestions were implemented. Moreover, ACM introduction led to a significant decrease in hemoglobin fluctuation (intrapatient standard deviation decreased from 0.95 g/dl to 0.83 g/dl). Thus, ACM support helped improve anemia outcomes of hemodialysis patients, minimizing erythropoietic-stimulating agent use with the potential to reduce the cost of treatment.

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Anemia management in end-stage kidney disease patients (ESKD) receiving hemodialysis (HD) and treated by erythropoietic-stimulating agents (ESAs) is an important task for nephrologists who are asked to achieve several objectives at the same time, at both the patient and facility levels.

Briefly, hemoglobin (Hb) values should be maintained in a quite narrow target window, in a stable manner, using the smallest possible ESA doses. These are all delicate objectives on their own because of the following:

(i) Hb targets have changed over time, as well as in special clinical situations[1–4]; target levels have been reduced and the window has been narrowed (10–12 g/dl), according to the results of recent randomized trials[5–7] and a large meta-analysis.[8] In clinical practice, it is difficult to maintain Hb levels within such narrow range due to substantial inter- and intrapatient variability.[9–11]

(ii) Hb variability needs to be minimized to prevent undesired effects in fragile patients,[11–13] but this is not a trivial issue considering that, as reported, for example, by Berns *et al.*,[10] 1-month Hb values exhibit the greatest degree of variability, with ∼20% of the patients showing Hb variations >3.3 g/dl.

(iii) The ESA dose has to be reduced to mitigate ESA-related hazards.[14] The U.S. Food and Drug Administration recommends administering the lowest ESA dose needed to avoid recurrent blood transfusions.

(iv) Cost-related issues have also emerged as an additional hurdle, questioning the cost-benefit value of ESAs to treat anemia in dialysis patients.[15]

Successfully achieving all of these requirements can place an additional workload on nephrologists caring for a large number of patients; this is aggravated by the complexity and heterogeneity of the ESKD population, presenting with different medical profiles and diverse, possibly changing, sensitivity to ESAs, leading to the need for more precise, personalized dose adjustments. Given the importance of anemia management for the patient's well-being, developing interactive guided clinical tools to support the physician's work would be a favorable advancement.

In recent years, a variety of predictive algorithms based on sophisticated modeling approaches have been proposed to

predict Hb levels in ESKD patients and to offer a personalized treatment in line with the predicted Hb trend[16–19]; their promising results suggest that such approaches can be powerful tools for anemia management in dialysis patients. Some of these algorithms have also been tested in a clinical setting, albeit often in relatively small cohorts of patients.[20–23]

In a previous work, we built our anemia modeling approach and evaluated its reliability and predictive value in a retrospective study involving a large number of ESKD patients treated in the Fresenius Medical Care clinical network.[24] Motivated by our encouraging results, we decided to deploy our decision support system, the Anemia Control Model (ACM), in 3 pilot clinics as part of the daily care routine of a large population of unselected patients. Complementing the i.v. iron therapy based on internal protocols following best practice guidelines (see Supplementary Appendix), the ACM computes the ESA dose suggestions based on the following 2 components: (i) an artificial neural network model that uses patients' clinical data as input and predicts future Hb concentrations[24] and (ii) an algorithm that, simulating the effect of different ESA doses, determines the optimal prescription to achieve the desired Hb targets.

The purpose of this study was to determine how ACM support can affect outcomes of anemia management in daily clinical practice, with the aims of maintaining Hb targets and reducing Hb variability and ESA consumption in ESKD patients.

RESULTS

Outcome at the dialysis facility level

Baseline characteristics of ESKD patients participating in the study are presented in Table 1; 653 patients were included in the control phase and 640 in the observation phase, for a total of 752 patients participating in at least 1 phase. These 2 populations were quite similar in both clinical characteristics and lab data at baseline. In the control phase, therapy for anemia was devised by the attending physicians, following established best clinical practices and internal network Standard Operating Procedures (Supplementary Appendix), without ACM support; during the observation phase, physicians were provided with ACM recommendations.

Anemia outcomes are presented in Table 2. During ACM-guided care, darbepoetin consumption decreased by 25% (from 40 [interquartile range, 100] to 30 [interquartile range, 100] μg/month), whereas the percentage of Hb values within the target range increased by 6% (from 70.6% to 76.6%) in the entire population. It should be noted, however, that only a portion of Hb values in the observation phase resulted from *accepted* ACM suggestions; others were obtained after rejecting the suggestion or independently of the ACM (as the patient was ACM ineligible at the time). Therefore, to more closely evaluate ACM value, we consider anemia outcomes when suggestions were actually confirmed. Both figures show a more decisive improvement (83.2% Hb values on target; median darbepoetin = 20 [interquartile range, 80] μg/month). Between the study phases, the percentage of Hb values over target decreased (from 17% to 9.8%), whereas the percentage of Hb values below target range slightly increased (from 12.3% to 13.6%); however, when considering only lab tests resulting from accepted ACM suggestions, both percentages actually decreased (to 7.5% and 9.3%, respectively). Iron consumption also decreased across the 2 periods.

Adverse events, i.e., mortality, cardiovascular events, hospitalizations, and transfusions, were also extracted. All these events tended to decrease after ACM entrance (Table 2).

Table 1 | Patients characteristics in the 2 study periods in the facility level analysis

Characteristics	Control phase	Observation phase	*P*-value
Total no. of patients	653	640	
Age, yr, mean ± SD	63.65 ± 15.45	63.86 ± 15.46	0.81[b]
Male, no. (%)	409 (62.6)	397 (62.0)	0.86[a]
Patients initiating RRT, no. (%)	70 (10.7)	62 (9.7)	0.58[a]
Comorbidities, no. (%)			
Coronary artery disease	59 (9.0)	56 (8.8)	0.92[a]
Congestive heart failure	147 (22.5)	145 (22.7)	1.00[a]
Peripheral vascular disease	187 (28.6)	184 (28.8)	1.00[a]
Cerebrovascular disease	114 (17.5)	115 (18.0)	0.83[a]
Chronic pulmonary disease	96 (14.7)	92 (14.4)	0.87[a]
Diabetes	196 (30.0)	188 (29.4)	0.81[a]
Charlson Comorbidity Index, mean ± SD	5.98 ± 3.98	5.76 ± 3.86	0.28[b]
Causes of kidney disease, no. (%)			
Diabetes	141 (21.6)	140 (21.9)	0.95[a]
Hypertension	123 (18.8)	126 (19.7)	0.72[a]
Chronic glomerulonephritis	143 (21.9)	133 (20.8)	0.64[a]
Urinary obstruction/chronic interstitial nephritis	11 (1.7)	10 (1.6)	1.00[a]
Polycystic kidney disease	39 (6.0)	41 (6.4)	0.82[a]
Other	196 (30.0)	190 (29.7)	0.90[a]
Vascular access, no. (%)			
Fistula	427 (65.4)	418 (65.3)	1.00[a]
Catheter	130 (19.9)	121 (18.9)	0.67[a]
Graft	96 (14.7)	101 (15.8)	0.64[a]
Treatment modality, no. (%)			
HDF online	608 (93.1)	595 (93.0)	1.00[a]
High-flux HD	32 (4.9)	36 (5.6)	0.62[a]
Other	13 (2.0)	9 (1.4)	0.52[a]
Laboratory test value			
Hemoglobin, g/dl, mean ± SD	11.32 ± 1.08	11.19 ± 1.07	0.02[b]
Ferritin, ng/ml, median (IQR)	526.90 (365.88)	580.65 (325.10)	0.03[c]
TSAT, %, median (IQR)	29.77 (13.14)	30.50 (12.47)	0.21[c]
Albumin, g/dl, mean ± SD	3.90 ± 0.45	3.92 ± 0.38	0.43[b]
Calcium, mg/dl, mean ± SD	8.79 ± 0.60	8.92 ± 0.62	<0.001[b]
Phosphate, mg/dl, mean ± SD	4.37 ± 1.07	4.30 ± 1.02	0.21[b]
Potassium, mmol/l, mean ± SD	4.95 ± 0.65	4.92 ± 0.62	0.45[b]
PTH, ng/l, median (IQR)	276.45 (240.13)	271.70 (245.00)	0.85[c]
Overhydration, l, mean ± SD	1.83 ± 1.62	1.91 ± 1.40	0.35[b]
eKTV, mean ± SD	1.67 ± 0.42	1.70 ± 0.31	0.54[b]
spKTV, mean ± SD	1.90 ± 0.47	1.94 ± 0.36	0.45[b]

Overhydration was estimated by bioimpedance by means of the body composition monitor. For laboratory tests, mean/median values were computed for each patient and then averaged across all patients.
Ch Int, chronic interstitial; eKTV/spKTV, equilibrated/single-pool Kt/V; HD, hemodialysis; HDF, hemodiafiltration; PTH, parathyroid hormone; RRT, renal replacement therapy; TSAT, transferrin saturation index.
[a]Fisher exact test.
[b]Unpaired *t* test.
[c]Wilcoxon test.