SUPPLEMENTARY DATA

Supplementary methods

The main methodological approach is summarized in the main manuscript; the following section provides the analytical formulae and additional technical details.

Continuous variables are presented as median [interquartile range] and categorical variables as counts and percentages. Included and excluded admissions were compared using standardized mean differences.

In the primary continuous models, ΔCr and ΔHb were winsorized at the 1st and 99th percentiles to reduce the influence of extreme values. ΔCr was modeled with restricted cubic splines using 4 quantile-based knots located at the 5th, 35th, 65th, and 95th percentiles. ΔHb was entered linearly in the primary specification. Sensitivity analyses allowed nonlinear modeling of ΔHb and replacement of ΔHb by ΔHct or by Strauss-estimated plasma volume contraction, calculated from paired hemoglobin and hematocrit values obtained at the timepoint of peak creatinine rise.

Mortality and composite endpoints were analyzed using Cox proportional hazards models with robust standard errors. First all-cause and first HF rehospitalizations were analyzed using Fine-Gray subdistribution hazard models to account for the competing risk of death. For mortality and secondary endpoints, interaction was assessed by likelihood-ratio tests comparing models with and without the ΔCr×ΔHb interaction block.

From the fitted models, we estimated adjusted ratios associated with the observed ΔHb interquartile-range increase (+1.3 g/dL), calculated as the difference between the 75th and 25th percentiles of ΔHb in the analytic cohort and used as the primary reporting contrast, and with the secondary +0.5 and +1.0 g/dL contrasts. These effects are expressed as smooth functions of ΔCr, with confidence intervals derived by the delta method.

A beneficial range was defined as the contiguous ΔCr interval in which the upper 95% confidence interval remained below 1.0. Nonsignificant regions, in which the 95% confidence interval crossed 1.0, were interpreted as safety regions. Because adverse high-ΔCr regions extended to the upper observed

tail of the distribution, harm was summarized as a harm threshold, defined as the lower ΔCr boundary above which the lower 95% confidence interval remained above 1.0.

Internal validation for mortality was performed with 200 bootstrap resamples to estimate the apparent and optimism-corrected Harrell c-index and the mean calibration slope. Full-range ΔHb response curves at fixed creatinine anchors are shown in supplementary figure S2, observed exposure distributions in supplementary figure S11, and sensitivity analyses using ΔHct and Strauss-estimated plasma volume contraction in supplementary tables S7-S8.

Analytical formula for benefit, safety, and harm:

For mortality, the adjusted effect of a ΔHemoglobin increase h at a given ΔCreatinine value x can be written as:

• HR(h, x) = exp(h * eta(x))

where eta(x) is the restricted cubic spline interaction function of ΔCreatinine estimated from the fitted model. In the final model:

• eta(x) = -0.09643 - 0.41063*x + 0.30966*s1(x) + 2.74874*s2(x)

with restricted cubic spline knots for Δcreatinine at:

• -0.32, 0.00, 0.16, and 0.64 mg/dL

Because positive Δhemoglobin increments enter the model as a multiplicative scaling of the same eta(x), the sign of log(HR) is invariant across positive Δhemoglobin values. Therefore, the location of the Δcreatinine beneficial range, the surrounding safety regions, and the high-Δcreatinine harm threshold is unchanged for Δhemoglobin +0.5, +1.0 g/dL, and the observed IQR increase of 1.3 g/dL; only the magnitude of the adjusted ratio changes. Because ΔHb enters the primary model linearly, increasing positive hemoglobin increments change the magnitude of the adjusted ratio but do not move the creatinine benefit/safety/harm boundaries shown in the main figures.

Baseline eGFR and baseline hemoglobin were included because the same absolute ΔCr or ΔHb may have different clinical meanings depending on the patient's starting renal function or hematologic status. This adjustment was intended to reduce confounding by baseline disease severity and starting laboratory values. However, because these variables are related to the exposure definitions, collinearity and partial over-adjustment cannot be excluded; therefore, adjusted estimates should be interpreted as conditional associations rather than causal effects.

Table S1. STROBE checklist for cohort studies and where each item is addressed in the clean manuscript.

Caption. Checklist content follows the journal STROBE template for cohort studies. The last column specifies where and how each recommendation is addressed in the main manuscript.

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
Title and abstract			
	1	(a) Indicate the study design with a commonly used term in the title or the abstract.	Title and Abstract. The title states the study topic, and the Abstract Methods begins: "We conducted a retrospective cohort study..."
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found.	Abstract: Background, Methods, Results, and Conclusions summarize the design, cohort dates, sample, events, main interaction test, safety windows, and conclusions.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.	Introduction paragraphs 1-3 explain ADHF, worsening renal function, hemoconcentration, pseudo-WRF, and why a continuous interaction approach was needed instead of binary thresholds.

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
Objectives	3	State specific objectives, including any prespecified hypotheses.	End of the Introduction. The manuscript states the two main aims: quantify the ΔCr-by-ΔHb interaction for mortality and extend the framework to rehospitalization outcomes.
Methods			
Study design	4	Present key elements of study design early in the paper.	Methods: Study design and data source. The study is described as a retrospective observational cohort using routinely collected clinical data.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	Methods: Study design and population. The blinded manuscript identifies a tertiary-care center and the inclusion period from January 1, 2014 to December 31, 2021; the identifying institution is supplied separately in the REC first-page file.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	Methods: Population and outcomes. Eligibility was based on consecutive ADHF admissions with final discharge diagnosis of acute heart failure; follow-up time and censoring are explicitly

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
			defined. Cohort selection is also shown in supplementary figure S1.
		(b) For matched studies, give matching criteria and number of exposed and unexposed.	Not applicable. This was not a matched cohort study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods: Exposures and phenotypes, Outcomes, and Covariates. ΔCr, ΔHb, phenotype definitions, mortality, rehospitalization endpoints, and the prespecified confounders are explicitly defined.
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	Methods: Exposures and phenotypes, outcomes, and covariates. The manuscript states that routinely collected in-hospital laboratory data were used, defines ΔCr and ΔHb from admission-based laboratory trajectories, and describes biomarker transformations and endpoint timing.

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
Bias	9	Describe any efforts to address potential sources of bias.	Methods: Covariates and Statistical analysis; Results: missing data and analytic sample; Limitations. The manuscript uses prespecified adjustment, evaluates included versus excluded patients with SMDs, and discusses residual confounding and selection bias in Limitations.
Study size	10	Explain how the study size was reached.	Methods: Population. The study size was determined by all eligible contemporary admissions in the predefined time window; the final analytic sample is derived through the cohort flow.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	Methods: Statistical analysis and Exposures and phenotypes. Continuous variables are summarized as median [IQR]; ΔCr and ΔHb are winsorized; ΔCr is modeled with restricted cubic splines; ΔHb is continuous in the primary model; phenotype cutoffs are used only for descriptive analyses.

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding.	Methods: statistical analysis. The manuscript details Cox models, Fine-Gray models, negative binomial models, bootstrap internal validation, Δ-method estimation, and the prespecified confounder adjustment set.
		(b) Describe any methods used to examine subgroups and interactions.	Methods: statistical analysis; Results. The manuscript specifies the ΔCr-by-ΔHb interaction, phenotype-based descriptive analyses, and endpoint-specific interaction curves.
		(c) Explain how missing data were addressed.	Methods: statistical analysis; Results: missing data and analytic sample. A complete-case strategy was used, and included vs excluded patients were compared in supplementary table S3; the overall sample derivation is shown in supplementary figure S1.
		(d) If applicable, explain how loss to follow-up was addressed.	No separate loss-to-follow-up analysis was required. Time-to-event, competing-risk, and recurrent-event models used

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
			administrative censoring as defined in Methods: outcomes.
		(e) Describe any sensitivity analyses.	Methods: Statistical analysis and Results. The manuscript states that nonlinear ΔHb sensitivity analyses were performed and did not materially improve fit; technical comparison files are provided in the supplementary technical folder. Supplementary Tables S7-S8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed.	Results: Missing data and analytic sample; Supplementary Figure S1. The manuscript reports 2335 eligible admissions, 2082 with ΔCr and ΔHb available, and 2043 complete-case admissions analyzed.
		(b) Give reasons for non-participation at each stage.	Results: Missing data and analytic sample; supplementary figure S1. Exclusions are attributed mainly to

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
			missing serial laboratory trajectories and, secondarily, missing covariates.
		(c) Consider use of a flow diagram	Addressed in supplementary figure S1 (PRISMA-style cohort flowchart).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders.	Results: Baseline characteristics; table 1; supplementary table S4 The manuscript provides demographic, clinical, laboratory, and phenotype-stratified baseline data.
		(b) Indicate number of participants with missing data for each variable of interest.	Results: Missing data and analytic sample; supplementary figure S1 and supplementary table S3. Missingness is reported through the cohort flow and complete-case comparison, rather than as a separate variable-by-variable missingness table.
		(c) Summarize follow-up time (eg, average and total amount).	Results: Patient flow and baseline characteristics; table 1. Mortality interaction.
Outcome data	15*	Report numbers of outcome events or	Results: Mortality and rehospitalization sections; table 1 and table 2. Numbers of

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
		summary measures over time.	deaths, first all-cause rehospitalizations, first HF rehospitalizations, and follow-up summaries are reported.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.	Unadjusted summaries appear in table 1 and supplementary table S5. Adjusted estimates with 95%CIs are shown in table 2, table 3, figures 1-5, and supplementary figures S3-S9. The prespecified confounders and rationale are described in Methods: Exposures, outcomes, and covariates, and Statistical analysis.
		(b) Report category boundaries when continuous variables were categorized	Methods: Exposures and phenotypes. The descriptive phenotype cutpoints are stated explicitly: WRF as $\Delta Cr \geq 0.3$ mg/dL and hemoconcentration as $\Delta Hb > 0$ g/dL.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	Absolute 1-year risks are reported descriptively in table 2 and supplementary table S8. The main inferential analyses remain time-to-event relative measures (HR, sHR, IRR).

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
Other analyses	17	Report other analyses done, eg analyses of subgroups and interactions, and sensitivity analyses.	Results: Rehospitalization and composite endpoints; supplementary tables S3-S5 and S7-S9; supplementary technical files. The manuscript reports interaction analyses, phenotype-stratified analyses, competing-risk analyses, recurrent-event analyses, calibration summaries, and nonlinear ΔHb sensitivity analyses.
Discussion			
Key results	18	Summarize key results with reference to study objectives.	Discussion opening paragraph directly restates the main findings in relation to the study objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	Limitations section. The manuscript discusses observational design, residual confounding, selection bias, measurement limitations in ΔCr and ΔHb, and external confirmation needs.
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Discussion and Conclusions. The manuscript interprets the safety-window findings cautiously, places them in prior

Section or item	Item No.	Recommendation	Where and how addressed in the main manuscript
		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	literature, and avoids treating them as therapeutic targets.
Generalisability	21	Discuss the generalizability (external validity) of the study results.	Limitations and Conclusions. The manuscript notes the single-center design and states that confirmation in independent cohorts is needed.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	Reported in the separate REC first-page submission file. The final funding statement should be completed there according to the authors' declaration, or explicitly state no funding.

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Table S2. Software environment and R packages used for data processing, statistical analyses, and figure generation

Component	Version	Role
R	4.5.2	Statistical computing environment
rms	8.1.1	Regression modeling strategies, validation, calibration, predict and bplot
Hmisc	5.2.5	Harrell support package used by rms
survival	3.8.3	Survival models, concordance and Kaplan-Meier estimation
MASS	7.3.65	Negative binomial regression
cmprsk	2.2.12	Competing-risk regression and cumulative incidence functions
ggplot2	4.0.2	Figure generation
jsonlite	2.0.0	JSON export
scales	1.4.0	Scaling and axis labels for figures
stats	4.5.2	Core statistical functions
utils	4.5.2	CSV input/output and general utilities

R, R statistical computing environment.

Packages are listed with the versions used in the final analytical workflow.

Table S3. Included vs excluded sample comparison using standardized mean differences

Variable	Included	Excluded	SMD
Age, y	77.0 [69.0-83.0]	79.0 [68.0-84.0]	−0.06
Male sex	1177 (57.6)	160 (54.8)	0.06
Calendar year	2017.0 [2016.0-2019.0]	2018.0 [2017.0-2019.0]	−0.26
Systolic BP, mmHg	136.0 [120.0-153.0]	135.0 [120.0-151.0]	0.09
Heart rate, bpm	90.0 [74.2-110.0]	90.0 [75.0-111.0]	−0.06
eGFR, mL/min/1.73m²	58.0 [41.4-77.2]	56.4 [39.3-79.6]	0.02
Sodium, mmol/L	139.0 [136.0-141.0]	138.0 [136.0-140.2]	0.05
Hemoglobin at admission, g/dL	12.4 [11.0-13.7]	12.4 [11.1-13.9]	−0.03
NT-proBNP, pg/mL	4099.0 [2023.0-8628.5]	4477.0 [2357.8-8247.6]	0.03
CA125, U/mL	54.9 [23.0-115.0]	50.0 [23.0-112.5]	0.06
C-reactive protein, mg/dL	17.0 [10.4-28.0]	18.1 [11.4-26.6]	0.04
Diuretic dose at admission	60.0 [60.0-80.0]	60.0 [60.0-80.0]	−0.00
Diabetes	910 (44.5)	100 (35.2)	0.19
Hypertension	1598 (78.2)	213 (75.0)	0.08

Variable	Included	Excluded	SMD
COPD	376 (18.4)	53 (18.2)	0.01
Ischemic heart disease	558 (27.3)	70 (25.3)	0.05
Valvular heart disease	760 (37.2)	114 (43.2)	−0.12
Peripheral edema	1376 (67.4)	185 (65.6)	0.04
Pleural effusion	1051 (51.4)	126 (45.2)	0.13
Death	548 (26.8)	60 (20.5)	0.15
First all-cause rehospitalization	1104 (54.0)	124 (42.5)	0.23
First HF rehospitalization	628 (30.7)	77 (26.4)	0.10

BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SMD, standardized mean difference.

The data are presented as median [interquartile range] or No. (%).Standardized mean differences are shown for the variables used to compare patients retained in the complete-case analytic cohort vs excluded patients.

Table S4. Baseline characteristics by phenotype

Characteristic	No WRF/No HC	HC only	WRF only	Pseudo-WRF
No.	886	763	213	181
Age, y	77.0 [69.0-83.0]	77.0 [68.0-82.0]	79.0 [71.0-85.0]	77.0 [69.0-82.0]
Male sex	56.4%	56.1%	62.0%	64.6%
eGFR, mL/min/1.73 m^2	57.6 [41.8-75.2]	61.4 [44.6-80.4]	48.0 [31.8-68.7]	56.9 [41.2-77.8]
SBP, mmHg	135.0 [120.0-152.0]	134.9 [117.0-150.5]	142.8 [125.0-167.0]	140.0 [126.0-155.0]
Heart rate, bpm	88.0 [74.0-110.0]	92.0 [75.0-115.0]	90.0 [75.0-110.0]	90.0 [74.0-109.0]
NT-proBNP, pg/mL	4197.5 [2212.0-9010.5]	3760.0 [1818.0-7537.5]	5800.0 [2742.0-13208.0]	3700.0 [1825.0-7736.0]
CA125, U/mL	55.0 [23.0-119.0]	56.0 [26.0-110.5]	42.0 [17.8-101.0]	57.0 [24.0-142.0]
Hemoglobin at admission, g/dL	12.7 [11.1-14.0]	12.2 [11.0-13.6]	12.3 [11.1-13.6]	12.2 [10.9-13.5]

Characteristic	No WRF/No HC	HC only	WRF only	Pseudo-WRF
Creatinine at admission, mg/dL	1.1 [0.9-1.5]	1.0 [0.8-1.4]	1.3 [1.0-1.8]	1.1 [0.9-1.4]
Δcreatinine (max), mg/dL	0.0 [−0.1 to 0.1]	0.0 [−0.1 to 0.2]	0.5 [0.4-0.7]	0.4 [0.3-0.6]
Δhemoglobin (max), g/dL	-0.6 [−1.1 to −0.3]	0.7 [0.3-1.2]	−0.7 [−1.3 to −0.3]	0.8 [0.4-1.5]
Diabetes	44.2%	45.3%	45.5%	41.4%

eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WRF, worsening renal function; HC, hemoconcentration.

Phenotypes were defined according to the cross-classification of worsening renal function and hemoconcentration.

Table S5. Unadjusted outcomes by phenotype

Phenotype	No.	1-year mortality, %	1-year first all-cause rehospitalization, cumulative incidence, %	1-year first HF rehospitalization, cumulative incidence, %	Mean total rehospitalizations	Mean HF rehospitalizations
No WRF/no HC	886	20.1	55.9	34.2	1.36	0.63
HC only	763	15.1	49.2	26.0	1.14	0.47
WRF only	213	20.3	55.8	31.3	1.39	0.53
Pseudo-WRF	181	17.6	54.1	26.5	1.59	0.58

HF, heart failure; WRF, worsening renal function; HC, hemoconcentration.

One-year event risks are presented by phenotype. Rehospitalization percentages correspond to 1-year cumulative incidence under the competing risk of death.

Table S6. Adjusted phenotype associations

Group	Effect measure	Adjusted ratio (95%CI)	*P*
Mortality (Cox)			
HC only	HR	0.85 (0.70-1.04)	.107
WRF only	HR	0.82 (0.60-1.11)	.200
Pseudo-WRF	HR	1.07 (0.80-1.44)	.636
First all-cause rehospitalization			
HC only	sHR	0.87 (0.76-1.00)	.043
First HF rehospitalization			
HC only	sHR	0.78 (0.65-0.94)	.009
First all-cause rehospitalization			
WRF only	sHR	1.09 (0.89-1.34)	.389
First HF rehospitalization			
WRF only	sHR	0.85 (0.64-1.13)	.272
First all-cause rehospitalization			
Pseudo-WRF	sHR	1.04 (0.83-1.30)	.717
First HF rehospitalization			
Pseudo-WRF	sHR	0.82 (0.61-1.11)	.195
Total rehospitalization count (NegBin)			

Group	Effect measure	Adjusted ratio (95%CI)	*P*
HC only	IRR	0.83 (0.73-0.95)	.008
WRF only	IRR	1.07 (0.87-1.32)	.508
Pseudo-WRF	IRR	1.09 (0.87-1.35)	.462
HF rehospitalization count (NegBin)			
HC only	IRR	0.77 (0.63-0.95)	.013
WRF only	IRR	1.02 (0.75-1.39)	.905
Pseudo-WRF	IRR	0.91 (0.65-1.28)	.601

HR, hazard ratio; IRR, incidence rate ratio; sHR, subdistribution hazard ratio; WRF, worsening renal function; HC, hemoconcentration.

Adjusted phenotype contrasts are shown relative to the reference phenotype (No WRF/No HC).

Table S7. Sensitivity analysis replacing Δhemoglobin with Δhematocrit

Contrast	ΔCreatinine target (mg/dL)	Effect measure	Adjusted ratio (95% CI)	*P*
Mortality				
Interaction between Δcreatinine spline and Δhematocrit		LRT	LR=3.51; df=3	.319
Observed Δhematocrit IQR (+4.8 percentage points)	0.1	HR	0.86 (0.74-1.00)	.048
Observed Δhematocrit IQR (+4.8 percentage points)	0.3	HR	0.86 (0.71-1.05)	.143
Observed Δhematocrit IQR (+4.8 percentage points)	0.5	HR	0.92 (0.74-1.13)	.425
First all-cause rehospitalization				
Interaction between Δcreatinine spline and Δhematocrit		LRT	LR=2.06; df=3	.561
Observed Δhematocrit IQR (+4.8 percentage points)	0.1	sHR	0.88 (0.80-0.97)	.013
Observed Δhematocrit IQR (+4.8 percentage points)	0.3	sHR	0.93 (0.82-1.07)	.310

Contrast	ΔCreatinine target (mg/dL)	Effect measure	Adjusted ratio (95% CI)	*P*
Observed Δhematocrit IQR (+4.8 percentage points)	0.5	sHR	0.97 (0.84-1.12)	.651
First HF rehospitalization				
Interaction between Δcreatinine spline and Δhematocrit		LRT	LR=1.26; df=3	.738
Observed Δhematocrit IQR (+4.8 percentage points)	0.1	sHR	0.85 (0.74-0.96)	.011
Observed Δhematocrit IQR (+4.8 percentage points)	0.3	sHR	0.88 (0.73-1.05)	.160
Observed Δhematocrit IQR (+4.8 percentage points)	0.5	sHR	0.91 (0.75-1.12)	.375
Composite of death or first all-cause rehospitalization				
Observed Δhematocrit IQR (+4.8 percentage points)	0.1	HR	0.91 (0.83-1.01)	.065
Observed Δhematocrit IQR (+4.8 percentage points)	0.3	HR	0.94 (0.83-1.07)	.332
Observed Δhematocrit IQR (+4.8 percentage points)	0.5	HR	0.97 (0.84-1.11)	.630

HR, hazard ratio; LRT, likelihood-ratio test; sHR, subdistribution hazard ratio.

Ratios correspond to the adjusted association of the observed Δhematocrit interquartile-range increase at the indicated Δcreatinine target. Interaction tests are shown for mortality and the Fine-Gray rehospitalization models.

Table S8. Sensitivity analysis replacing ΔHemoglobin with Strauss-estimated plasma volume contraction

Contrast	ΔCreatinine target (mg/dL)	Effect measure	Adjusted ratio (95%CI)	*P*
Mortality				
Interaction between Δcreatinine spline and Strauss-estimated plasma volume contraction		LRT	LR=9.60; df=3	.022
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.1	HR	0.88 (0.77-1.01)	.065
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.3	HR	0.87 (0.74-1.02)	.096
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.5	HR	1.02 (0.85-1.23)	.828
First all-cause rehospitalization				
Interaction between Δcreatinine spline and Strauss-estimated plasma volume contraction		LRT	LR=10.19; df=3	.017

Contrast	ΔCreatinine target (mg/dL)	Effect measure	Adjusted ratio (95%CI)	*P*
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.1	sHR	0.87 (0.79-0.95)	.002
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.3	sHR	0.90 (0.80-1.01)	.084
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.5	sHR	1.01 (0.88-1.14)	.936
First HF rehospitalization				
Interaction between Δcreatinine spline and Strauss-estimated plasma volume contraction		LRT	LR=4.96; df=3	.174
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.1	sHR	0.83 (0.74-0.94)	.003
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.3	sHR	0.86 (0.73-1.01)	.062

Contrast	ΔCreatinine target (mg/dL)	Effect measure	Adjusted ratio (95%CI)	*P*
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.5	sHR	0.98 (0.81-1.19)	.832
Composite of death or first all-cause rehospitalization				
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.1	HR	0.90 (0.82-0.98)	.015
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.3	HR	0.91 (0.81-1.02)	.104
Observed Strauss-estimated plasma volume contraction IQR (+17.5%)	0.5	HR	1.01 (0.89-1.14)	.869

HR, hazard ratio; LRT, likelihood-ratio test; sHR, subdistribution hazard ratio.

The Strauss exposure was defined at the timepoint of peak in-hospital creatinine rise using the paired hemoglobin and hematocrit values available at that same timepoint. Ratios correspond to the adjusted association of the observed Strauss interquartile-range increase at the indicated Δcreatinine target. Interaction tests are shown for mortality and the Fine-Gray rehospitalization models.

Table S9. eGFR-stratified sensitivity analysis

eGFR stratum	Endpoint	n	LR	P	ΔCr 0.10	ΔCr 0.30	ΔCr 0.50	Benefit range	Harm threshold
eGFR < 60 mL/min/1.73 m²	Mortality	1081	8.72	0.033	0.91 (0.76 - 1.08)	0.85 (0.69 - 1.06)	1.01 (0.80 - 1.26)	None identified	0.90
eGFR < 60 mL/min/1.73 m²	All-cause rehospitalization	1081	5.99	0.112	0.93 (0.82 - 1.06)	0.94 (0.79 - 1.11)	1.04 (0.87 - 1.24)	None identified	0.86
eGFR < 60 mL/min/1.73 m²	HF rehospitalization	1081	1.38	0.710	0.90 (0.76 - 1.06)	0.89 (0.71 - 1.12)	0.97 (0.74 - 1.29)	None identified	None identified
eGFR < 60 mL/min/1.73 m²	Death/all-cause rehospitalization	1081	5.54	0.136	0.95 (0.84 - 1.07)	0.94 (0.80 - 1.11)	1.04 (0.87 - 1.24)	None identified	0.89
eGFR ≥ 60 mL/min/1.73 m²	Mortality	962	5.55	0.136	0.82 (0.63 - 1.07)	1.01 (0.75 - 1.36)	1.26 (0.90 - 1.78)	None identified	None identified

eGFR ≥ 60 mL/min/1.73 m²	All-cause rehospitalization	962	1.40	0.705	0.84 (0.73 - 0.98)	0.86 (0.71 - 1.03)	0.93 (0.74 - 1.15)	0.06-0.22	None identified
eGFR ≥60 mL/min/1.73 m²	HF rehospitalization	962	2.21	0.531	0.76 (0.62 - 0.92)	0.76 (0.59 - 1.00)	0.87 (0.65 - 1.18)	0.03-0.31	None identified
eGFR ≥60 mL/min/1.73 m²	Death/all-cause rehospitalization	962	1.58	0.664	0.86 (0.75 - 0.99)	0.86 (0.72 - 1.03)	0.93 (0.76 - 1.15)	0.09-0.21	None identified

ΔCr, creatinine change; ΔHb, hemoglobin change; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LR, likelihood-ratio statistic; sHR, subdistribution hazard ratio.

Models were refitted within baseline eGFR strata (<60 vs ≥60 mL/min/1.73 m²), omitting eGFR spline terms from within-stratum adjustment. Adjusted ratios correspond to the primary observed ΔHb IQR contrast (+1.3 g/dL). Interaction tests compare models with and without the ΔCrxΔHb block (df=3).

Figure S1. PRISMA-style cohort selection flowchart.

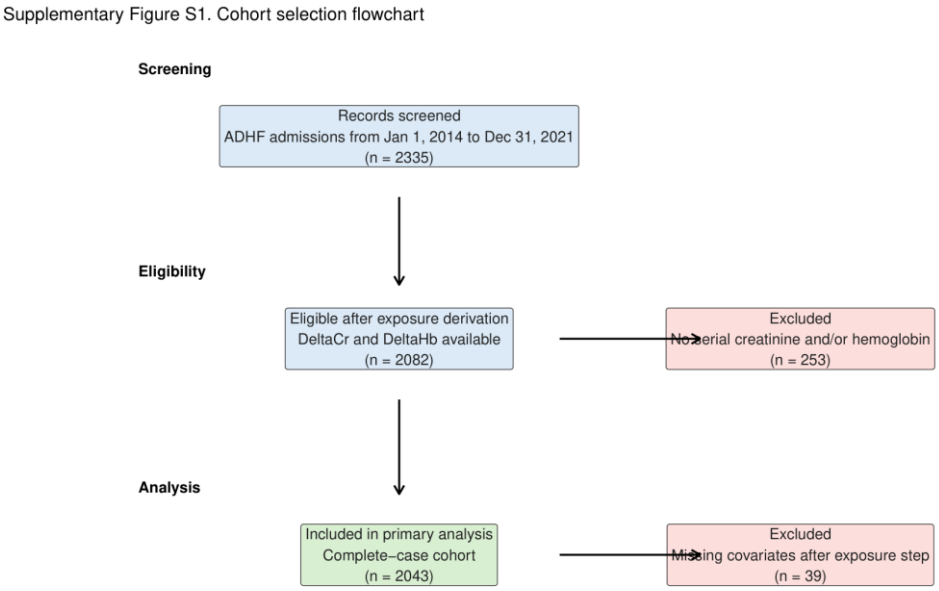

Figure S2. Full-range continuous ΔHb-response curves across fixed ΔCr anchors.

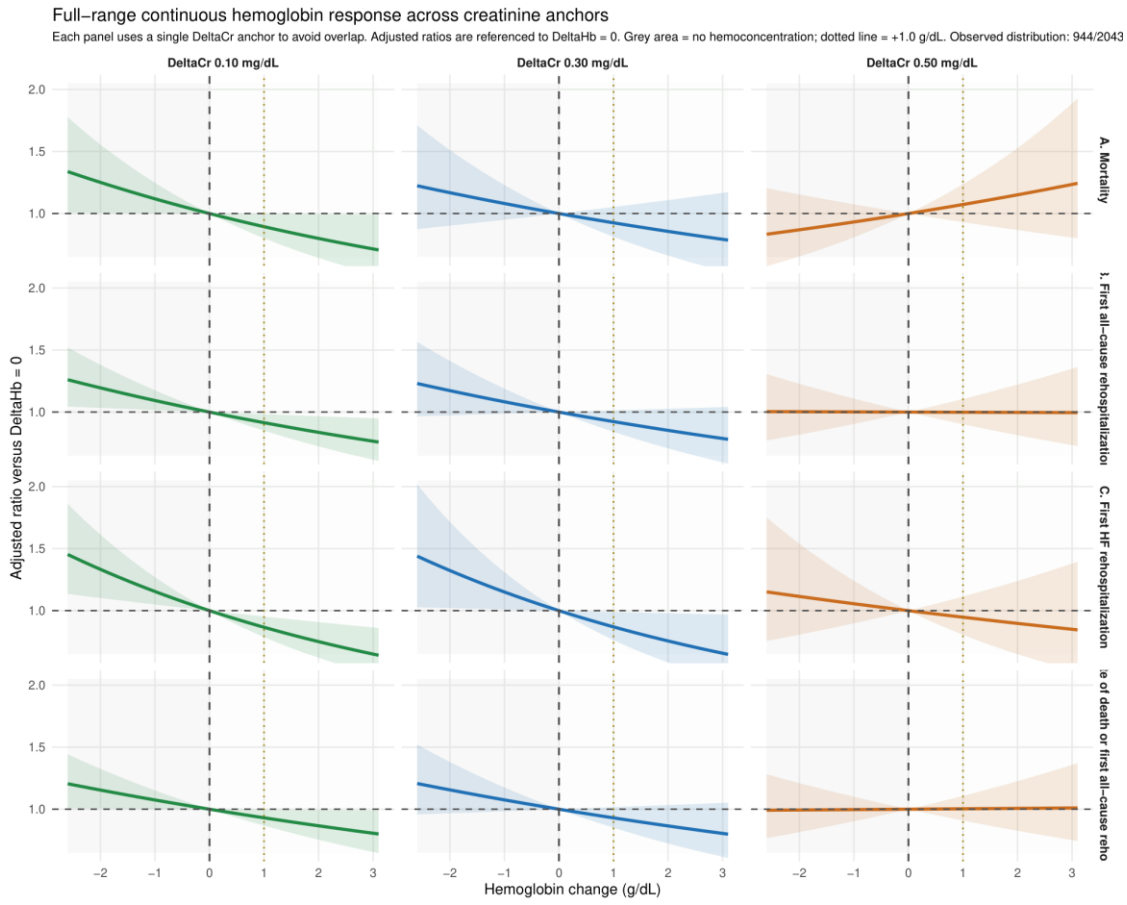

Figure S3. Cumulative incidence of first all-cause rehospitalization by phenotype.

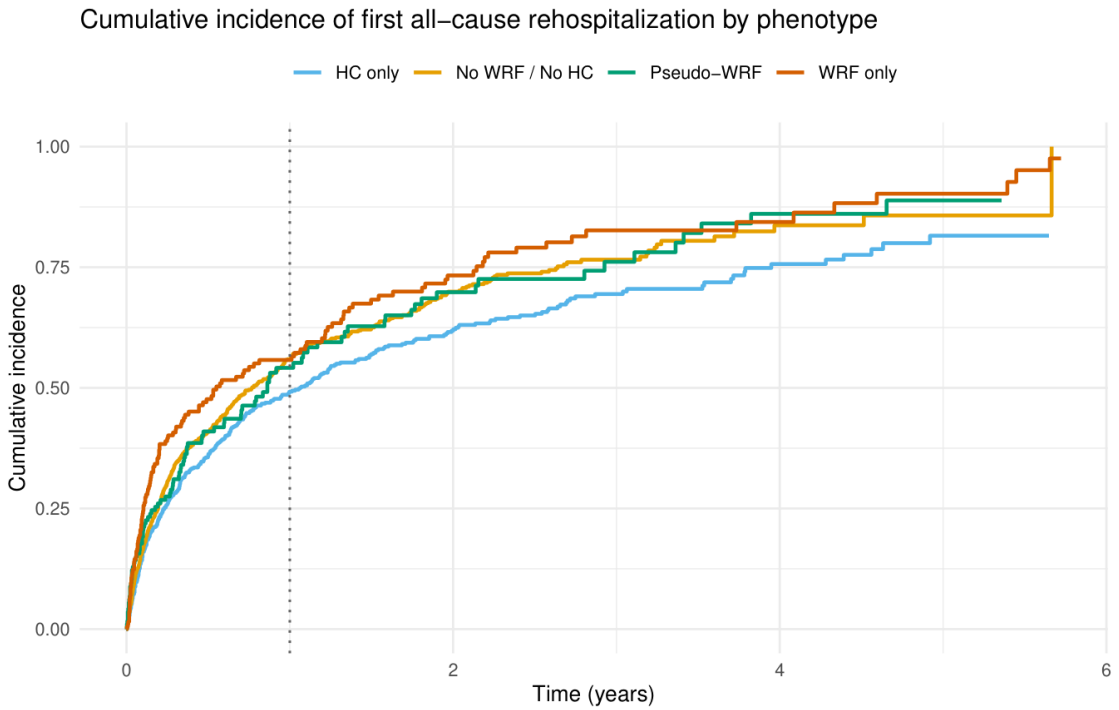

Figure S4. Cumulative incidence of first HF rehospitalization by phenotype.

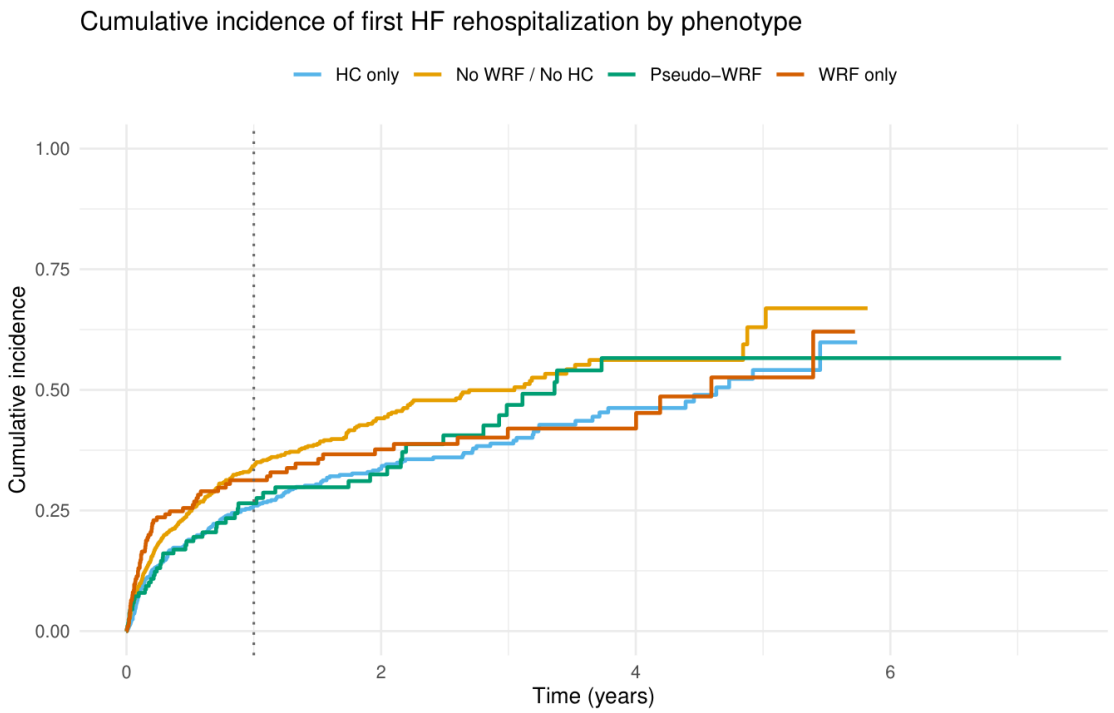

Figure S5. Mortality joint ΔHb-ΔCr surface in the positive quadrant.

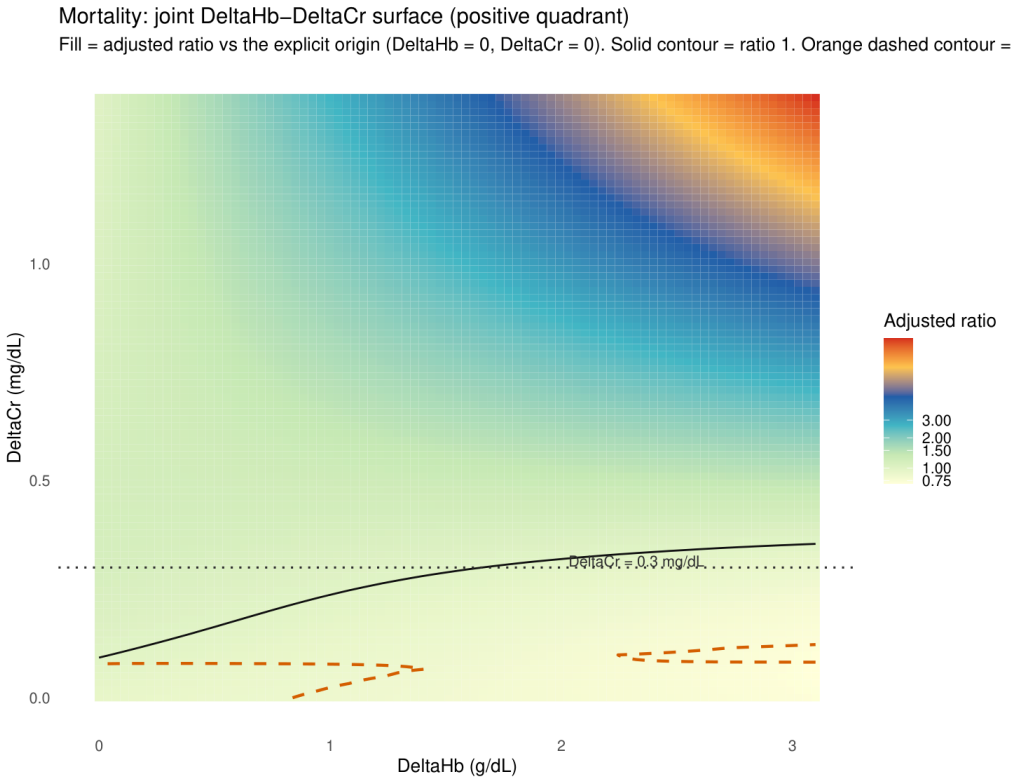

Figure S6. Harrell bplot of the mortality joint surface.

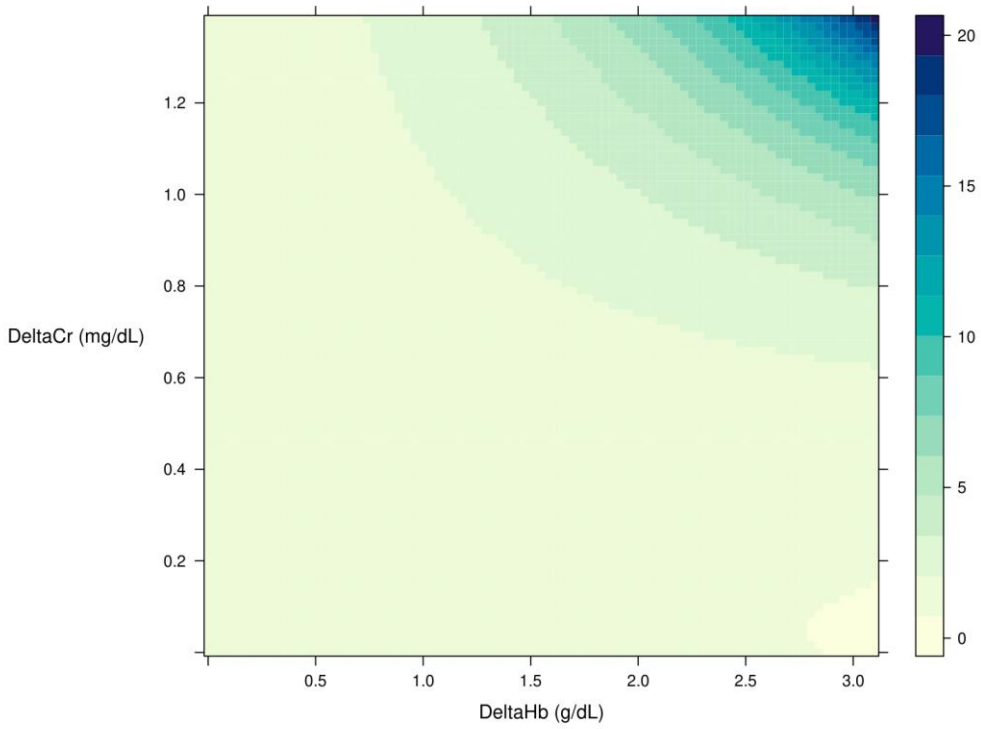

Figure S7. Composite-any joint ΔHb-ΔCr surface in the positive quadrant.

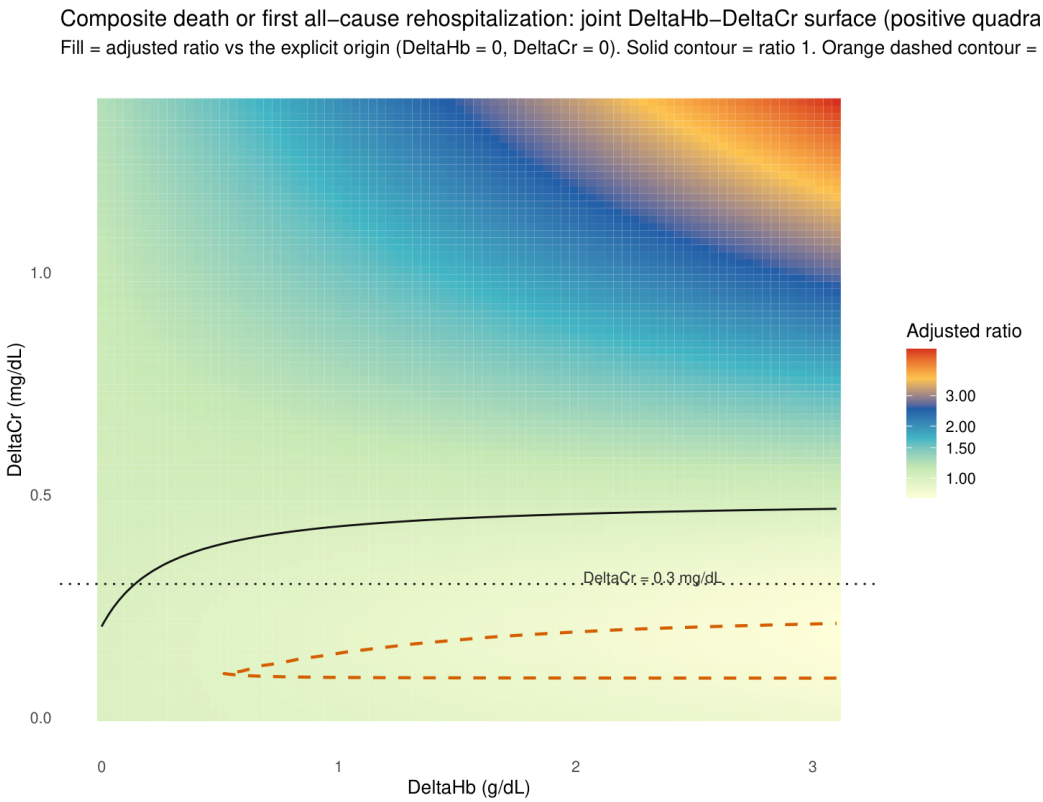

Figure S8. Harrell bplot of the composite-any joint surface.

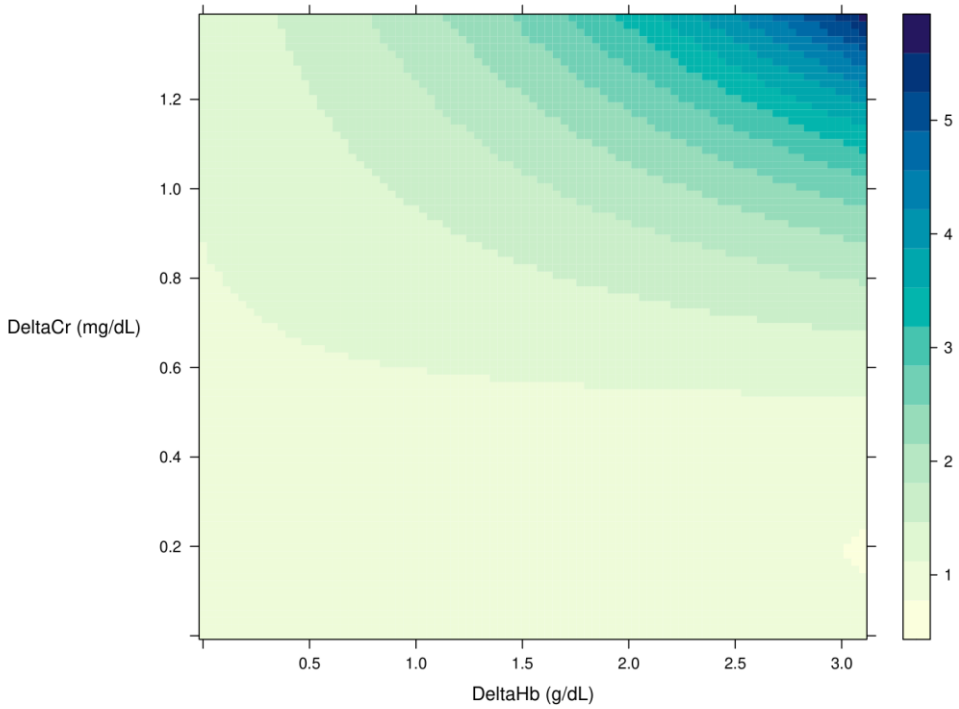

Figure S9. Composite-heart failure joint ΔHb-ΔCr surface in the positive quadrant.

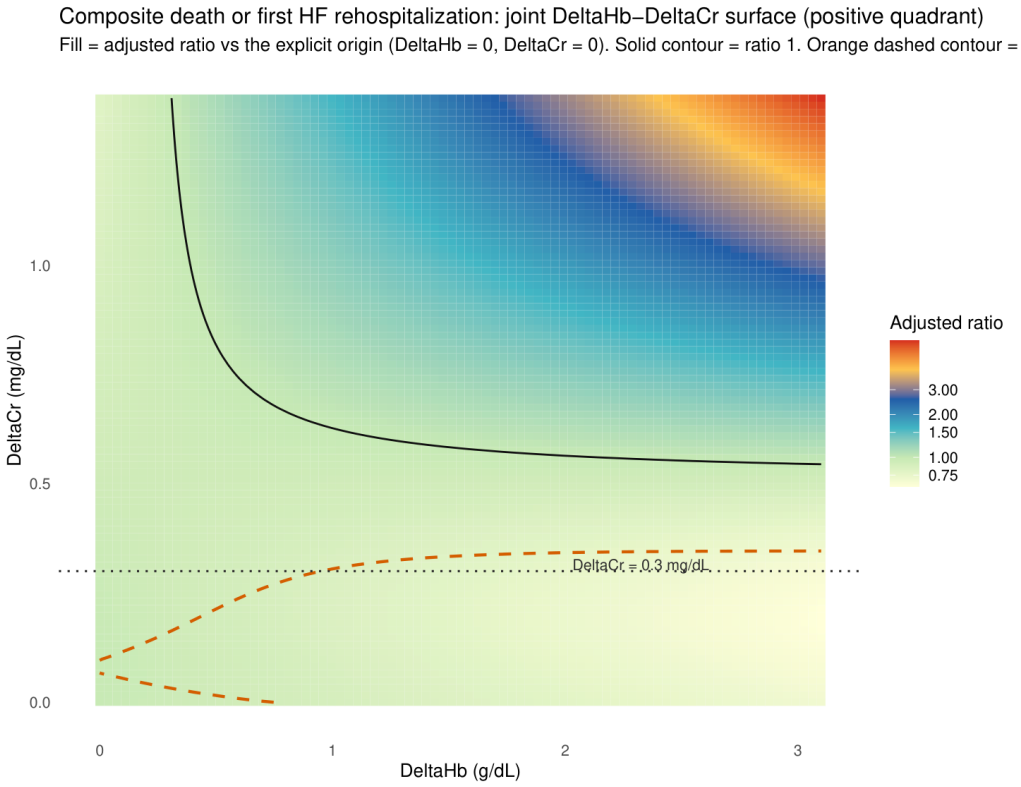

Figure S10. Harrell bplot of the composite-HF joint surface.

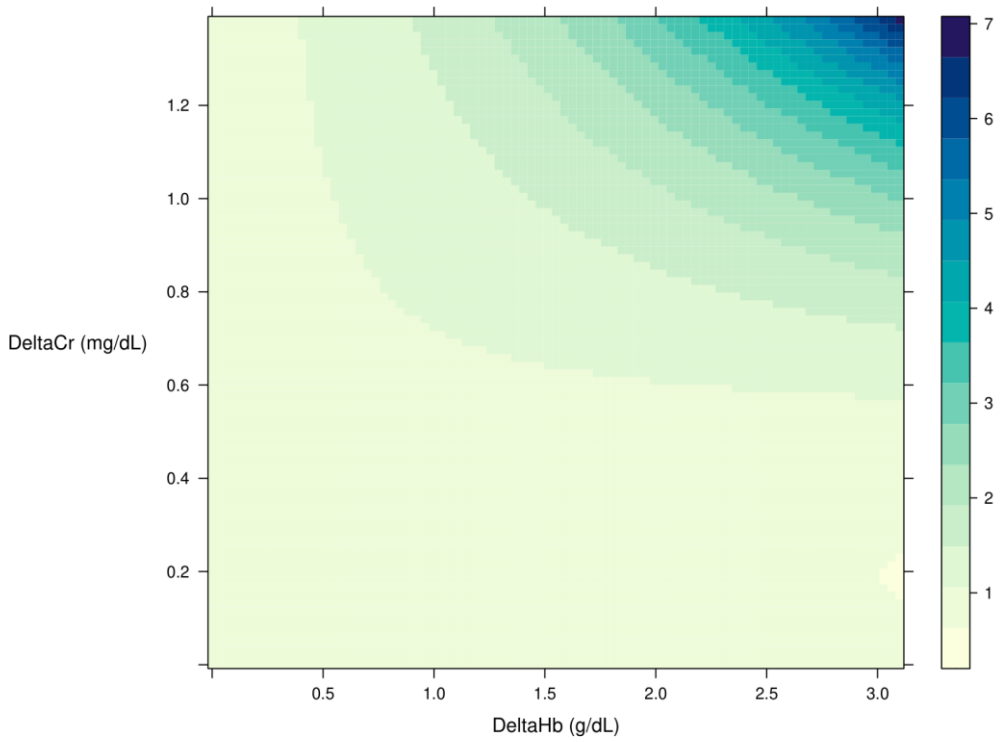

Figure S11. Observed distributions of Δcreatinine and Δhemoglobin with beneficial ranges and harm thresholds overlaid.