Prescription of medical therapy and postdischarge outcomes in patients hospitalized with HFrEF: insights from the ICARUS registry

Supplementary Data

***Table S1**. Per-variable missingness and imputation methods*

Section	Variable	No. observed	% missing	Imputation method
Demographics	Age, y	3839	0.0	Not imputed (complete)
Demographics	Sex, male	3839	0.0	Not imputed (complete)
Demographics	Enrollment year	3839	0.0	Not imputed (complete)
HF severity	LVEF, %	3838	0.0	Not imputed (complete)
HF severity	NT-proBNP, pg/mL	1903	50.4	PMM
Etiology	Chagas etiology	3839	0.0	Not imputed (complete)
Etiology	Ischemic etiology	3839	0.0	Not imputed (complete)
Comorbidities	Hypertension	3839	0.0	Not imputed (complete)
Comorbidities	Diabetes	3839	0.0	Not imputed (complete)
Comorbidities	CKD	3839	0.0	Not imputed (complete)
Comorbidities	CAD	3839	0.0	Not imputed (complete)
Comorbidities	Dyslipidemia	3839	0.0	Not imputed (complete)

Section	Variable	No. observed	% missing	Imputation method
Comorbidities	Hypothyroidism	3839	0.0	Not imputed (complete)
Comorbidities	Pulmonary hypertension	3839	0.0	Not imputed (complete)
Arrhythmia	Atrial fibrillation	3839	0.0	Not imputed (complete)
Arrhythmia	Left bundle branch block	3839	0.0	Not imputed (complete)
Prior GDMT	Prior beta-blocker	3839	0.0	Not imputed (complete)
Prior GDMT	Prior RAASi	3839	0.0	Not imputed (complete)
Prior GDMT	Prior MRA	3839	0.0	Not imputed (complete)
Prior GDMT	Prior SGLT2i	3839	0.0	Not imputed (complete)
Vitals	SBP, mmHg	3798	1.1	PMM
Vitals	DBP, mmHg	3790	1.3	PMM
Vitals	Heart rate, bpm	3830	0.2	PMM
Labs	Serum potassium, mEq/L	3526	8.2	PMM
Labs	Serum creatinine, mg/dL	1969	48.7	PMM
Body composition	BMI, kg/m²	3670	4.4	PMM

BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Multiple imputation by chained equations (MICE) was performed with m = 30 imputations and 10 iterations. Predictive mean matching was used for continuous variables and logistic regression for binary variables. All covariates, outcomes, and the treatment indicator were included in the

imputation model. Results were pooled across 30 imputed datasets using Rubin’s rules. Fraction of missing information (FMI) for primary outcomes: composite 27.5%; all-cause mortality 27.2%; readmission 27.4%; CV death 26.9%. Variables not captured in the ICARUS registry (hemoglobin, sodium, loop diuretic dose, structured congestion score at discharge) are listed for transparency; these will be incorporated in the planned multicenter extension.

Table S2. Percentage of patients with each laboratory value recorded, by enrollment year

Enrolment year	N	Creatinine	NT-proBNP	Potassium
2022	564	99	53	93
2023	915	99	38	92
2024	1057	27	54	91
2025	1163	19	52	93
2026	140	0	59	89

Table S3. Missingness by treatment group and 30-day outcome status

Variable (admission)	Overall	Quadruple	Incomplete	30-d death	Alive
NT-proBNP	50.4	47.4	58.1	51.6	50.4
Serum creatinine	48.7	48.4	49.5	51.6	48.6
Serum potassium	8.2	7.5	9.8	4.6	8.3
Systolic BP	1.1	0.6	2.3	1.3	1.1
FRAIL score	24.6	23.1	28.6	25.5	24.6

The data are expressed as percentages.

Table S4. Predictors of missingness

Predictor	Missing creatinine OR (95%CI); *P*	Missing NT-proBNP OR (95%CI); *P*
Enrolment year, per y	9.3 (8.1-10.7); < .001	0.88 (0.83-0.93); < .001
30-day death	1.02 (0.61-1.73); .93	1.12 (0.77-1.62); .55
Quadruple therapy	0.95 (0.77-1.17); .61	0.69 (0.59-0.79); < .001

Table S5. Variance inflation factors for the 26-covariate propensity-score model

PS covariate	Variance inflation factor
prior_mra	4.940
prior_bb	4.611
prior_sglt2i	4.183
prior_raasi	4.109
hta	2.056
af	1.608
has_arrhythmia	1.481
diabetes	1.461
log10_probnp	1.437
creatinina	1.406
cad	1.400
enrollment_year	1.374
ischemic	1.364
ckd	1.337
fevi_imp	1.331
nyha_imp	1.262
age	1.249
sbp	1.215

PS covariate	Variance inflation factor
dyslipidemia	1.181
chagas	1.177
hypothyroid	1.156
potasio	1.148
bmi	1.118
male	1.093
hr	1.091
pulm_htn	1.051

af, atrial fibrillation; bb, beta-blocker; bmi, body mass index; cad, coronary artery disease; ckd, chronic kidney disease; hr, heart rate; htn, hypertension; lvef, left ventricular ejection fraction; mra, mineralocorticoid receptor antagonist; probnp, N-terminal pro-B-type natriuretic peptide; nyha, New York Heart Association; PS, propensity score; raasi, renin-angiotensin-aldosterone system inhibitor; sbp, systolic blood pressure; sglti, sodium-glucose cotransporter 2 inhibitor.

Variance inflation factor (VIF) for each covariate in the final 26-covariate propensity-score logistic regression. All VIFs are below 5. Diastolic blood pressure was excluded from the PS model after sensitivity assessment: if DBP were included, its VIF would be 2.08 and SBP VIF would rise from 1.22 to 2.21 (SBP-DBP Pearson correlation r = 0.671).

Table S6. Covariate balance before and after propensity score matching

Covariate	SMD before matching	SMD after matching
Logit propensity score	0.621	0.004
Creatinine	0.485	0.010
Potassium	0.298	0.022
LVEF	0.252	0.017
CKD	0.216	0.022
log10(NT-proBNP)	0.202	0.026
Prior SGLT2i	0.118	0.026
Prior MRA	0.111	0.027
Ischemic	0.108	0.038
Any arrhythmia	0.107	0.025
Systolic BP	0.099	0.066
Hypothyroidism	0.095	0.020
Diabetes	0.086	0.028
Chagas	0.060	0.030
Age	0.058	0.022
NYHA class	0.055	0.020
Prior RAASi	0.040	0.023
Male sex	0.038	0.028
BMI	0.035	0.029
Heart rate	0.034	0.027
Enrolment year	0.033	0.000
Dyslipidemia	0.020	0.029
Atrial fibrillation	0.020	0.024
Pulmonary hypertension	0.014	0.037
CAD	0.013	0.027
Prior beta-blocker	0.009	0.024
Hypertension	0.002	0.023

BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Table S7. Time-stratified 30-day mortality (PS-matched cohort)

Time period	Deaths (IT)	Deaths (QT)	Death rate (IT)	Death rate (QT)	IT vs QT HR (95% CI)	*P*
Days 0-7	38	32	5.49 per 1000 person-d	1.75 per 1000 person-da	3.10 (1.94-4.96)	< .001
Days 7-30	23	50	2.05 per 1000 person-d	1.66 per 1000 person-d	1.24 (0.76-2.03)	.39

IT, incomplete therapy; HR, hazard ratio; QT (quadruple therapy).
Cox proportional hazards regression with time-stratified interaction (treatment × period) on the PS-matched cohort. The hazard ratio is presented as incomplete therapy vs quadruple therapy.

Table S8. Eligibility-restricted subgroup analyses (PS-matched)

Subgroup	No. (QT)	No. (IT)	Mortality events QT/IT	Mortality RR (95%CI), *P*	Composite events QT/IT	Composite RR (95%CI), *P*
eGFR ≥ 30	2592	822	69/43	0.55 (0.33-0.94), .029	437/194	0.71 (0.57-0.87), .001
eGFR ≥ 45	2187	643	48/32	0.54 (0.29-1.01), .052	354/145	0.68 (0.52-0.89), .005
K ≤ 5.0	2363	814	71/44	0.57 (0.33-0.98), .043	394/187	0.71 (0.56-0.88), .002
SBP ≥ 100	2270	870	67/47	0.64 (0.36-1.16), .145	371/206	0.69 (0.55-0.87), .002

Subgroup	No. (QT)	No. (IT)	Mortality events QT/IT	Mortality RR (95%CI), *P*	Composite events QT/IT	Composite RR (95%CI), *P*
Non-Chagas + eGFR ≥ 30 + K ≤ 5.0 + SBP ≥ 100	1585	478	39/19	Underpowered (events < 30/arm)	235/91	0.72 (0.51-1.03), .072

eGFR, estimated glomerular filtration rate; IT, incomplete therapy; K, potassium; PS, propensity score; QT, quadruple therapy; SBP, systolic blood pressure.

Exploratory analyses pre-specified after peer-review comments. eGFR computed via CKD-EPI 2021 race-free equation from imputed creatinine, age, and sex. Prespecified threshold: ≥ 30 events per arm required for inferential interpretation of relative risk. Subgroups below this threshold are reported descriptively only.

Table S9. Key-laboratory-complete and observed-creatinine eGFR subgroup sensitivity analyses

Analysis	No.	Events (comp/mort)	Composite RR (95%CI)	Mortality RR (95%CI)
Full cohort—imputed (reference)	3839	751/153	0.71 (0.58-0.88)	0.61 (0.37-1.01)
Key laboratory complete subset: observed creatinine + NT-proBNP + K + SBP	802	133/29	0.64 (0.40-1.04)	0.24 (0.10-0.57)
Crude (unmatched) in the same subset	802	133/29	0.65 (0.47-0.90)	0.30 (0.15-0.62)
eGFR ≥ 30—observed creatinine	1737	269/56	0.72 (0.50-1.03)	0.57 (0.26-1.24)
eGFR ≥ 30—imputed creatinine (supplementary table 8)	3414	—	0.71 (0.57-0.88)	0.55 (0.33-0.94)
eGFR ≥ 45—observed creatinine	1456	214/45	0.65 (0.43-0.98)	0.50 (0.22-1.15)
eGFR ≥ 45—imputed creatinine (supplementary table 8)	2830	—	0.68 (0.52-0.89)	0.54 (0.29-1.01)

Comp, composite endpoint, eGFR, estimated glomerular filtration rate; K, potassium; mort, mortality; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RR, risk ratio; SBP, systolic blood pressure.

All estimators used the primary 26-covariate propensity-score optimal full-matching approach, exact matching on enrollment year, a 0.2-SD caliper of the logit propensity score, and quasibinomial log-link risk ratios with CR2 cluster-robust standard errors. The key laboratory complete analysis required observed creatinine, NT-proBNP, potassium, and systolic blood pressure; other incompletely observed model covariates remained multiply imputed. The composite point estimate was similar to the full-cohort estimate, with wider uncertainty in the smaller subset. Because observed creatinine was concentrated in the period from 2022 to 2023, this subset was enriched for earlier enrolment (75% vs 39%). Observed-creatinine eGFR analyses produced similar point estimates but wider confidence intervals, reducing concern (without proving) that the subgroup findings were driven by creatinine imputation.

Table S10. PS-matched outcomes with and without frailty as the 27th covariate

Outcome	Primary PS (26 covariates) RR (95%CI)	Sensitivity PS (27 covariates incl. FRAIL) RR (95%CI)
All-cause mortality	0.61 (0.37-1.01)	0.61 (0.39-0.97)
CV death	0.57 (0.34-0.94)	0.57 (0.36-0.91)
All-cause readmission	0.76 (0.60-0.97)	0.76 (0.61-0.94)
Composite	0.71 (0.58-0.88)	0.71 (0.59-0.86)

CV, cardiovascular, PS, propensity score, RR, risk ratio.

Table S11. Sensitivity analysis restricted to patients with observed NT-proBNP

Outcome	Primary MI-pooled (n = 3839) RR (95%CI)	Observed NT-proBNP subset (n = 1903) RR (95%CI)	*P*
All-cause mortality	0.61 (0.37-1.01)	0.36 (0.19-0.69)	.002
CV death	0.57 (0.34-0.94)	0.34 (0.18-0.66)	.001
All-cause readmission	0.76 (0.60-0.97)	0.73 (0.55-0.97)	.030
Composite	0.71 (0.58-0.88)	0.62 (0.48-0.80)	< .001

CI, confidence interval; CV, cardiovascular; MI, multiple imputation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RR, risk ratio.

Sensitivity analysis restricted to the 1903 patients with directly observed NT-proBNP, performed to assess dependence of the primary results on NT-proBNP imputation. Other incompletely observed model covariates remained multiply imputed.

Table S12. δ-Adjustment (pattern-mixture) sensitivity analysis for departures from missing-at-random in serum creatinine and NT-proBNP

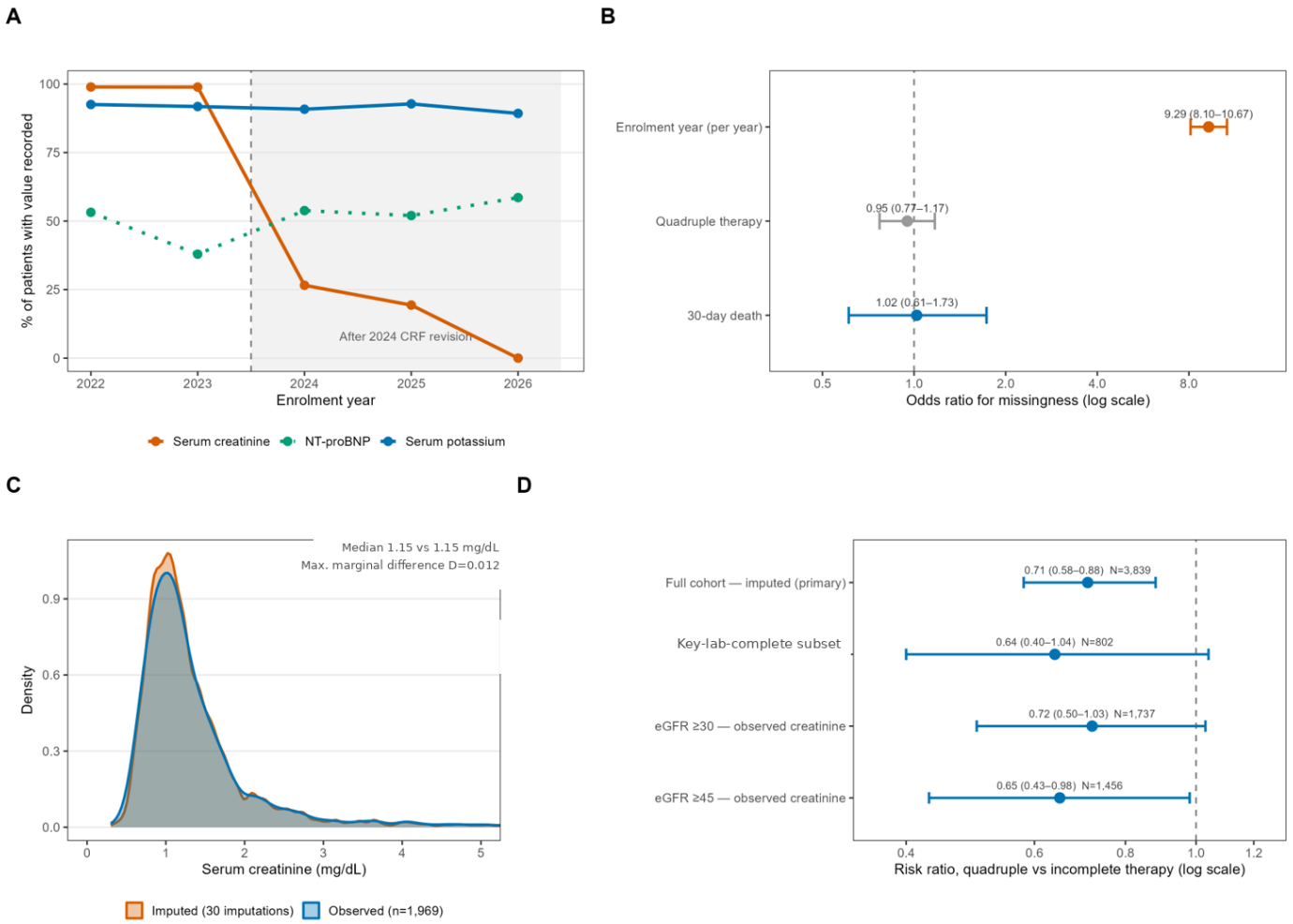
Assumed value of the missing data	30-d composite		30-d all-cause mortality	
	RR (95%CI)	*P*	RR (95%CI)	*P*
Serum creatinine—shift (mg/dL) added to imputed values				
0.5 mg/dL lower than MAR	0.72 (0.62-0.83)	< .001	0.63 (0.45-0.89)	.010
MAR (primary imputation)	**0.73 (0.63-0.84)**	**< .001**	**0.64 (0.45-0.91)**	**.012**
0.5 mg/dL higher	0.73 (0.63-0.84)	< .001	0.64 (0.45-0.91)	.013
1.0 mg/dL higher	0.73 (0.64-0.85)	< .001	0.64 (0.45-0.91)	.012
1.5 mg/dL higher (extreme)	0.74 (0.64-0.85)	< .001	0.64 (0.45-0.90)	.010
NT-proBNP—multiplicative shift applied to imputed values				
×0.5 (halved)	0.72 (0.63-0.83)	< .001	0.63 (0.45-0.90)	.010
MAR (primary imputation)	**0.73 (0.63-0.84)**	**< .001**	**0.64 (0.45-0.91)**	**.012**
×2	0.73 (0.63-0.84)	< .001	0.65 (0.46-0.92)	.014
×3.2	0.73 (0.63-0.84)	< .001	0.65 (0.46-0.92)	.015
×5 (extreme)	0.73 (0.63-0.84)	< .001	0.65 (0.46-0.92)	.016

MAR = missing at random; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RR = risk ratio (quadruple versus incomplete therapy).

Overlap-weighted treatment-only generalized linear models were pooled across 30 multiply imputed datasets using Rubin's rules; at $\delta = 0$, estimates reproduce the primary overlap-weighted analysis. Originally, missing values were shifted before re-estimation to examine specified departures from MAR. Estimates remained similar across the common-shift scenarios shown. These analyses address only the specified shifts and do not exclude differential or other unexamined missing-not-at-random mechanisms.

FIGURES

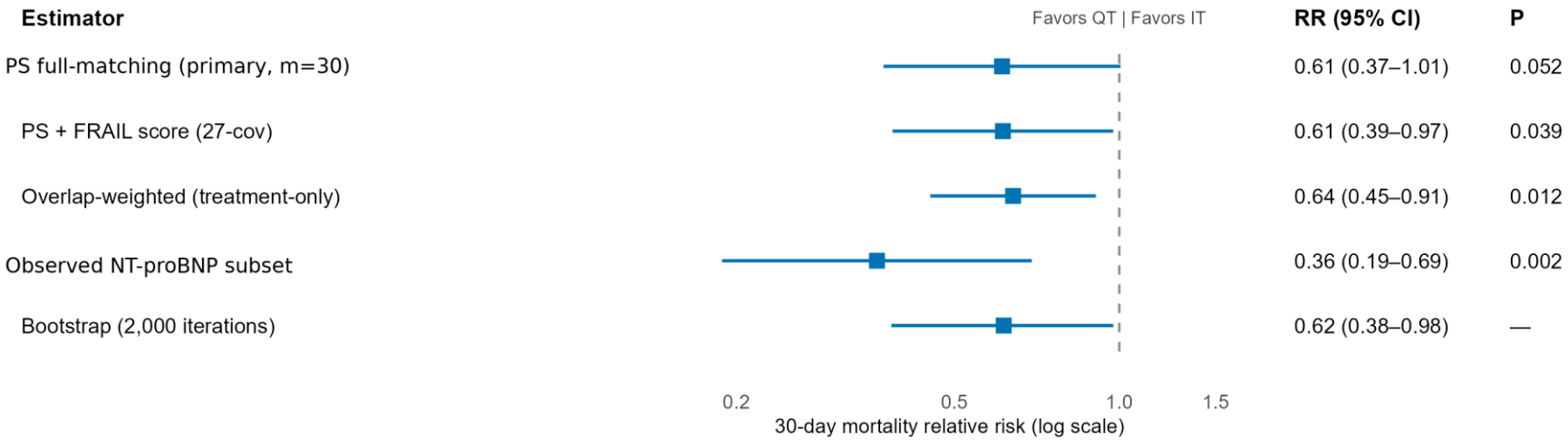
Figure S1. Serum-creatinine missingness analysis.



eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
A: percentage of patients with each admission laboratory value recorded, by enrolment year. B: multivariable logistic-regression odds ratios for missing serum creatinine: missingness was strongly associated with enrollment year and was not statistically associated with quadruple-therapy prescription or 30-day mortality. C: marginal kernel-density distributions of observed (n = 1969) and multiply imputed serum creatinine (pooled

across 30 imputations) were similar (median, 1.15 vs 1.15 mg/dL; maximum marginal distribution difference D = 0.012). D: Thirty-day composite risk ratios in the full imputed cohort, a key laboratory complete subset (observed creatinine, NT-proBNP, potassium, and systolic blood pressure), and eGFR-eligibility subgroups calculated using observed creatinine. Point estimates were similar, with wider uncertainty in the smaller observed data subsets.

Figure S2. Thirty-day mortality robustness panel.



IT, incomplete therapy; PS, propensity score, QT, quadruple therapy; RR, risk ratio.