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ORIGINAL RESEARCH

Concomitant Hepatorenal Dysfunction and Malnutrition in Valvular Heart Surgery: Long-Term Prognostic Implications for Death and Heart Failure

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BACKGROUND: Strategies to improve long-term prediction of heart failure and death in valvular surgery are urgently needed because of an increasing number of procedures globally. This study sought to report the prevalence, changes, and prognostic implications of concomitant hepatorenal dysfunction and malnutrition in valvular surgery.

METHODS AND RESULTS: In 909 patients undergoing valvular surgery, 3 groups were defined based on hepatorenal function (the modified model for end-stage liver disease excluding international normalized ratio score) and nutritional status (Controlling Nutritional Status score): normal hepatorenal function and nutrition (normal), hepatorenal dysfunction or malnutrition alone (mild), and concomitant hepatorenal dysfunction and malnutrition (severe). Overall, 32%, 46%, and 19% of patients were classified into normal, mild, and severe groups, respectively. Over a 4.1-year median follow-up, mild and severe groups incurred a higher risk of mortality (hazard ratio [HR], 3.17 [95% CI, 1.40–7.17] and HR, 9.30 [95% CI, 4.09–21.16], respectively), cardiovascular death (subdistribution HR, 3.29 [95% CI, 1.14–9.52] and subdistribution HR, 9.29 [95% CI, 3.09–27.99]), heart failure hospitalization (subdistribution HR, 2.11 [95% CI, 1.25–3.55] and subdistribution HR, 3.55 [95% CI, 2.04–6.16]), and adverse outcomes (HR, 2.11 [95% CI, 1.25–3.55] and HR, 3.55 [95% CI, 2.04–6.16]). Modified model for end-stage liver disease excluding international normalized ratio and controlling nutritional status scores improved the predictive ability of European System for Cardiac Operative Risk Evaluation (area under the curve: 0.80 versus 0.73, $P<0.001$) and Society of Thoracic Surgeons score (area under the curve: 0.79 versus 0.72, $P=0.004$) for all-cause mortality. One year following surgery (n=707), patients with persistent concomitant hepatorenal dysfunction and malnutrition (severe) experienced worse outcomes than those without.

CONCLUSIONS: Concomitant hepatorenal dysfunction and malnutrition was frequent and strongly linked to heart failure and mortality in valvular surgery.

Key Words: heart failure ■ hepatorenal dysfunction ■ malnutrition ■ risk-stratification ■ valvular surgery

Valvular interventions, either replacement or repair, remain the only definitive treatment to relieve symptoms and improve prognosis in patients with valvular heart disease (VHD).[1] The immediate improvement in symptoms may, however, be counteracted by the development of heart failure (HF) late after valvular surgery, which portends a dismal prognosis frequently overlooked by traditional risk-scoring

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CLINICAL PERSPECTIVE

What Is New?

- In patients with valvular heart disease, hepatorenal dysfunction, represented by the modified model for end-stage liver disease excluding international normalized ratio and nutritional status, by the Controlling Nutritional Status score, often coexist and are correlated with cardiac structure and function.
- Hepatorenal dysfunction and malnutrition are associated with an increased risk of heart failure and death after valvular surgery; beyond traditional cardiac surgery risk models, the modified model for end-stage liver disease excluding international normalized ratio and Controlling Nutritional Status scores provide incremental value for risk stratification in valvular surgery.
- Deterioration of hepatorenal function and nutritional status, along with their persistent dysfunction 1 year after valvular surgery, confer poor long-term prognosis.

What Are the Clinical Implications?

- Modified model for end-stage liver disease excluding international normalized ratio and Controlling Nutritional Status scores, comprising simple and objective parameters obtained during routine assessment, could aid the prognostication of conventional risk-scoring systems in valvular surgery.
- Pre- and postoperative clinical assessment can include an extracardiac workup to identify patients at high risk of adverse clinical outcomes.

Nonstandard Abbreviations and Acronyms

CKD-EPI	chronic kidney disease epidemiology collaboration
CONUT	controlling nutritional status
CVATS	Chinese Valvular Heart Disease Study
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
MELD-XI	modified model for end-stage liver disease excluding international normalized ratio
SHR	subdistribution hazard ratio
STS	Society of Thoracic Surgeons
TR	tricuspid regurgitation
VHD	valvular heart disease
ΔCONUT	1-year change in CONUT score
ΔMELD-XI	1-year change in MELD-XI score

models.[2] Indeed, while the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II and the Society of Thoracic Surgeons (STS) score are commonly used for risk stratification in valvular surgery,[3,4] they yield only modest discriminatory accuracy for predicting long-term mortality and HF.[5,6] Furthermore, these scoring systems tend to misclassify risk, particularly among high-risk individuals who are increasingly encountered in our aging population,[3,5,6] along with an increasing prevalence of cardiovascular risk factors that drive the epidemic of VHD globally.[7] As such, there is an urgent need to incorporate novel strategies to improve baseline risk stratification in patients with VHD.

Extracardiac manifestations, including end-organ dysfunction[8] and inflammation,[9] are unique mechanistic factors that represent different expressions of VHD. In this context, hepatorenal function and nutritional status have emerged as key prognostic determinants in VHD,[10–12] although current evidence[10,12–14] is limited to selected populations with short follow-up, or insufficient adjustment of concomitant risk factors and medications. No study has reported the phenotype of concomitant hepatorenal dysfunction and malnutrition, leaving their consequences and changes following surgery unexplored. We sought to investigate the prevalence, risk factors, and prognostic role of hepatorenal function and nutritional status, as well as their incremental value to established risk-stratification models in a large cohort of patients undergoing valvular surgery. Furthermore, we wanted to characterize the changes to hepatorenal function and nutritional status after valvular surgery to examine the role of longitudinal assessments in predicting adverse outcomes.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This was a retrospective observational study that included 1080 consecutive patients with VHD undergoing valvular surgery at Queen Mary Hospital, Hong Kong between November 2012 and January 2021. Patients who presented for surgery primarily because of VHD were prospectively recruited into the Chinese Valvular Heart Disease Study database. From this cohort, patients with comprehensive laboratory assessment within the 3 months before valvular surgery and with at least 1 year of follow-up were enrolled in the study. Patients with end-stage liver (n=17) and renal disease (n=9) were excluded. End-stage liver disease was defined by evidence of liver cirrhosis on abdominal

imaging with episodes of ascites, variceal hemorrhage, or hepatic encephalopathy, while end-stage renal disease was defined by an estimated glomerular filtration rate <15 mL/min per 1.73 m^2 requiring hemodialysis. Baseline demographics between patients who were included (n=909) and excluded (n=171) for the present study were similar, except for a higher prevalence of atrial fibrillation, HF, and dyslipidemia among included patients (Table S1). This study was part of the Chinese Valvular Heart Disease Study to evaluate the pattern, pathophysiology, and clinical outcomes of VHD in Chinese patients.[15] The study was approved by the Institutional Review Board of the West Cluster Hospital Authority of Hong Kong and written informed consents were obtained from all subjects.

Clinical and Echocardiographic Parameters

Conventional cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, atrial fibrillation, and smoking status), medical history (prior myocardial infarction and stroke), New York Heart Association functional class, comorbidities, and baseline medical therapy were reviewed based on electronic patient records and dispensing history at baseline visit. HF was diagnosed clinically based on signs and symptoms of volume overload with structural or functional abnormalities on transthoracic echocardiography. The cause of VHD was documented according to the predominant valvular lesion based on preoperative diagnosis and confirmed with surgical records. Left ventricular (LV) dimensions and systolic function, hemodynamics, and valvular lesion severity were assessed using an integrated approach based on M-mode, 2-dimensional and color, continuous- and pulsed-wave Doppler echocardiography according to American Society of Echocardiography guidelines.[16–18] Significant tricuspid regurgitation (TR) was defined as moderate or severe TR assessed using a multiparametric approach comprising qualitative, semiquantitative, and quantitative parameters.[18]

Laboratory Measurements

Preoperative blood data represented the most recent laboratory analysis within the 3 months before valvular surgery. The estimated glomerular filtration rate was derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. To evaluate changes in hepatorenal function and nutrition after valvular surgery, postoperative blood data were also collected 1 year following surgery.

Assessment of Hepatorenal Function

Hepatorenal function was assessed using the modified model for end-stage liver disease excluding international normalized ratio (MELD-XI) score, which was calculated as 5.11×ln(serum total bilirubin)+11.76×ln(serum creatinine)+9.44. To avoid a negative score, 1.0 mg/dL was established as the minimum value of total bilirubin and creatinine. MELD-XI score was selected as the principal measure of hepatorenal function because of its known association with clinical outcomes and its accurate reflection of hepatorenal function.[10,11,13,14]

Assessment of Nutritional Status

Patients were screened for malnutrition using the Controlling Nutritional Status score (CONUT) that takes account of serum albumin, cholesterol, and total lymphocyte count. A score of 0 to 1 is deemed normal; scores of 2 to 4, 5 to 8, and 9 to 12 reflect mild, moderate, and severe malnutrition, respectively. The CONUT score was chosen because of its superior prognostic value and discrimination ability compared with other nutritional indices used in prior studies.[12,19]

End Points and Follow-up

The end points of interest included all-cause mortality, cardiovascular death, HF hospitalization, and major adverse cardiac events (defined as the composite of death and HF hospitalization). HF admission was defined as having symptoms or signs of HF and being prescribed diuretics during hospitalization. Information pertaining to HF hospitalization and death was ascertained from a detailed review of medical records, and follow-up was complete for all patients.

Statistical Analysis

Continuous data are presented as median with interquartile range and categorical data as frequencies and proportions. Differences among groups were tested using χ^2 test for categorical variables and the Kruskal–Wallis H test for non-normally distributed continuous variables. The correlation between MELD-XI and CONUT scores was assessed by Spearman's Rho. Linear and logistic regression were applied to identify predictors of hepatorenal dysfunction and malnutrition at baseline and 1-year follow-up. Receiver-operating characteristic analysis was performed to determine the optimal cut-off of MELD-XI for predicting all-cause mortality based on the Youden index. Using this cut-off, patients were stratified according to the presence of hepatorenal dysfunction and malnutrition:

1. Normal: normal hepatorenal function and well-nourished
2. Mild: hepatorenal dysfunction or malnutrition
3. Severe: hepatorenal dysfunction and malnutrition

Time-to-event data are summarized using Kaplan–Meier statistics, and log-rank tests were used to

compare survival across groups. Cox proportional hazards regression analyses were conducted to identify predictors of mortality and adverse events, and the proportional hazards assumptions were confirmed using Schoenfeld residuals. Variance inflation factors were used to determine whether significant collinearity was present between MELD-XI and CONUT scores. To determine the relative prognostic importance of clinical covariates and risk scores, explainable log-likelihood (χ^2) was calculated for each predictor. The Grønnesby and Borgan test, likelihood ratio test, Akaike information criteria, and Bayesian information criteria were used to assess calibration of the adjusted models. The Fine-Gray model was used to account for mutually exclusive end points; all-cause mortality was considered as a competing risk for HF hospitalization and noncardiovascular death for cardiovascular death. The incremental prognostic value of hepatorenal function and nutritional status over traditional risk-stratification models was assessed by multivariate stepwise block analysis. Formal risk-reclassification analysis was performed by calculating increments in the Harrell *C*-statistics, continuous net reclassification improvement, and integrated discrimination improvement. Changes in MELD-XI (ΔMELD-XI) and CONUT (ΔCONUT) scores were calculated as the difference between baseline and follow-up scores.

All statistical analyses were performed using SPSS (Version 26.0, SPSS Inc) and R version 4.0.3. Statistical tests were 2-sided, and a *P* value <0.05 denoted statistical significance.

RESULTS

Patient Characteristics

All patients who met the study inclusion criteria formed the primary cohort (n=909). Patients with both pre- and postoperative laboratory indices of hepatorenal function and nutrition formed the secondary cohort (n=707) (Figure S1). Based on the optimal threshold of MELD-XI score derived from receiver-operating characteristic analysis (>12.43) and malnutrition defined by CONUT score (≥2), patients were stratified into 3 groups: 316 (35%) patients had normal hepatorenal function and were well-nourished (normal); 416 (46%) had hepatorenal dysfunction or malnutrition (mild); and 177 (19%) had hepatorenal dysfunction and malnutrition (severe). Baseline characteristics according to hepatorenal function and nutrition phenotypes are presented in Table 1. During a median follow-up of 4.1 years (interquartile range, 2.4 to 5 years), 101 (11%) patients died (54 [6%]) because of cardiovascular causes and 119 (13%) were hospitalized for HF.

Clinical Associations, Prognostic Impact, and Discrimination Capacity of Combined Hepatorenal Dysfunction and Malnutrition

Multiple markers of hepatic function (aspartate aminotransferase, alkaline phosphatase, total bilirubin, and albumin), renal function (estimated glomerular filtration rate), together with echocardiographic parameters of the left heart (left ventricular ejection fraction and LV mass), pulmonary artery systolic pressure, and TR became progressively abnormal from normal to severe hepatorenal dysfunction and malnutrition. Correlates of concomitant hepatorenal dysfunction and malnutrition (severe) were EuroSCORE II, STS score, LV mass, significant TR, and pulmonary artery systolic pressure (Table S2A). MELD-XI scores were modestly correlated with CONUT scores (R=0.36, *P*<0.001) without significant collinearity (mean variance inflation factor =1.17) (Figure S2).

A graded increase in mortality, cardiovascular death, HF hospitalization, and adverse outcomes was observed in patients from normal to severe groups, with a clear step-up in event risk for patients in the severe group (Figure 1; Tables S2B through S2D). This association remained consistent in fully adjusted models (Table 2) regardless of the type of valvular surgery performed (aortic valve replacement and mitral valve surgery; Tables S3A and S3B) and the cause of VHD (chronic rheumatic heart disease and non–chronic rheumatic heart disease; Tables S3C and S3D). Landmark analysis excluding 30-day mortality also yielded similar results (Table S4). Within the mild group, there were no significant differences in survival (92.3% versus 89.7%, *P*=0.530) and adverse outcomes (79.5% versus 78.0%, *P*=0.773) between the subgroup with hepatorenal dysfunction (n=39) and malnutrition alone (n=377) (Figure S3). The prevalence, clinical correlates, and prognostic implications of hepatorenal dysfunction and malnutrition alone are illustrated in Tables S5A through S6E. The MELD-XI score was the most important predictor of mortality while the CONUT score was the strongest predictor of adverse events (Figure S4). The adjusted models demonstrated good calibration for predicting both all-cause mortality and adverse events (Table S7).

The addition of the MELD-XI score provided incremental prognostic value (χ^2 increased by 69.5, *P*<0.001) and discrimination improvement by *C*-statistic (0.77 versus 0.73, *P*=0.035) over EuroSCORE II (Figure 2). Likewise, the addition of the CONUT score to EuroSCORE II significantly improved model fit (χ^2 increased by 48.7, *P*<0.001) and discrimination (*C*-statistic 0.78 versus 0.73, *P*=0.026). The continuous net reclassification improvement and integrated discrimination improvement for all-cause mortality also increased after adding MELD-XI (0.58 and 0.07,

Table 1. Baseline Characteristics of the Study Population According to Hepatorenal Function (MELD-XI score) and Nutritional Status (CONUT score)

Characteristics	Overall (n=909)	Normal (Normal hepatorenal function and well-nourished; n=316)	Mild (Hepatorenal dysfunction or malnutrition; n=416)	Severe (Hepatorenal dysfunction and malnutrition; n=177)	*P* value
Demographic and anthropometric characteristics					
Age, y	63 (57–69)	60 (54–65)†,‡	64 (57–71)*	65 (60–70)*	<0.001
Male	431 (47.4)	132 (41.8)‡	192 (46.2)‡	107 (60.5)*,†	<0.001
Height, cm	159 (153–166)	159 (154–165)	159 (153–166)	160 (153–166)	0.969
Weight, kg	58 (50–67)	61 (52–70)†,‡	57 (50–66)*	57 (49–67)*	0.002
Body mass index, kg/m^2	23.0 (20.6–25.6)	23.8 (21.3–25.9)†,‡	22.7 (20.2–25.5)*	22.6 (19.7–25.4)*	0.002
NYHA Class III/IV	69 (7.6)	18 (5.7)‡	24 (5.8)‡	27 (15.3)*,†	<0.001
Cardiovascular risk factors and cardiovascular disease					
Hypertension	290 (31.9)	78 (24.7)†,‡	146 (35.1)*	66 (37.3)*	0.003
Diabetes	165 (18.2)	27 (8.5)†,‡	83 (20.0)*,‡	55 (31.1)*,†	<0.001
Dyslipidemia	231 (25.4)	64 (20.3)†	120 (28.8)*	47 (26.6)	0.028
Smoking	178 (19.6)	65 (20.6)	71 (17.1)	42 (23.7)	0.150
Prior myocardial infarction	37 (4.1)	6 (1.9)	21 (5.0)	10 (5.6)	0.507
Prior stroke	82 (9.1)	16 (5.1)†,‡	42 (10.2)*	4 (13.7)*	0.004
Heart failure	393 (43.2)	114 (36.1)‡	171 (41.1)‡	108 (61.0)*,†	<0.001
Atrial fibrillation	487 (53.6)	134 (42.4)†,‡	231 (55.5)*,‡	122 (68.9)*,†	<0.001
Comorbidities					
Chronic obstructive pulmonary disease	52 (5.7)	13 (4.1)	28 (6.7)	11 (6.2)	0.304
Cancer	52 (5.7)	19 (6.0)	26 (6.3)	7 (4.0)	0.525
Laboratory examination					
Hemoglobin, g/dL	12.9 (11.6–14.0)	13.3 (12.5–14.4)†,‡	12.8 (11.6–14.0)*,‡	11.3 (9.9–12.9)*,†	<0.001
White blood cell count, ×10^9/L	5.9 (4.9–7.0)	6.0 (5.2–6.9)	5.9 (4.6–7.3)	5.7 (4.7–6.8)	0.287
Platelet count, ×10^9/L	189 (157–227)	200 (174–234)†,‡	185 (153–222)*,‡	170 (128–213)*,†	<0.001
Creatinine, mg/dL	0.92 (0.78–1.14)	0.86 (0.76–1.00)†,‡	0.89 (0.77–1.06)*,‡	1.38 (1.12–1.61)*,†	<0.001
eGFR, mL/min per 1.73 m^2	75.9 (60.9–90.1)	83.1 (72.8–95.1)†,‡	78.1 (65.7–90.7)*,‡	51.3 (36.9–61.5)*,†	<0.001
AST, U/L	27 (22–35)	26 (22–32)†,‡	27 (22–35)*,‡	30 (25–41)*,†	<0.001
ALT, U/L	21 (16–29)	22 (17–29)‡	21 (16–29)	20 (15–25)*	0.046
ALP, U/L	71 (58–90)	66 (55–83)†,‡	71 (58–87)*,‡	83 (64–124)*,†	<0.001
Total bilirubin, mg/dL	0.53 (0.75–1.14)	0.63 (0.47–0.84)†,‡	0.77 (0.56–1.08)*,‡	1.56 (0.80–2.20)*,†	<0.001
Total cholesterol, mg/dL	159 (134–188)	189 (167–211)†,‡	147 (128–169)*,‡	135 (116–154)*,†	<0.001
Albumin, g/dL	4.2 (4.0–4.4)	4.3 (4.1–4.5)†,‡	4.2 (4.0–4.4)*,‡	4.0 (3.7–4.3)*,†	<0.001
Valvular heart disease and echocardiographic variables					
MS ≥ moderate	229 (25.2)	81 (29.7)	109 (30.6)	39 (26.5)	0.657
MR ≥ moderate	411 (45.2)	149 (47.8)	170 (41.4)‡	92 (52.6)†	0.031
AS ≥ moderate	322 (35.4)	108 (38.3)	159 (41.7)	55 (34.6)	0.281
AR ≥ moderate	231 (25.4)	90 (30.3)	99 (24.5)	42 (24.1)	0.171
TR ≥ moderate	365 (40.2)	78 (24.7)†,‡	177 (42.5)*,‡	110 (62.5)*,†	<0.001
Chronic rheumatic heart disease	259 (28.5)	84 (26.6)	123 (29.6)	52 (29.4)	0.647
LV mass, g	224 (176–294)	221 (175–294)†,‡	219 (169–282)*,‡	249 (198–320)*,†	<0.001
LVEF, %	60 (55–60)	60 (55–60)‡	60 (55–60)‡	55 (50–60)*,†	<0.001
Preserved, ≥50%	763 (84.3)	278 (88.3)‡	348 (83.9)	137 (78.3)*	0.014
Midrange, 40%–49%	57 (6.3)	18 (5.7)	29 (7.0)	10 (5.7)	0.734
Reduced, <40%	55 (6.1)	11 (3.5)‡	24 (5.8)	20 (11.4)*	0.002

(*Continued*)

Table 1. Continued

Characteristics	Overall (n=909)	Normal (Normal hepatorenal function and well-nourished; n=316)	Mild (Hepatorenal dysfunction or malnutrition; n=416)	Severe (Hepatorenal dysfunction and malnutrition; n=177)	*P* value
PASP, mm Hg	40 (35–50)	40 (30–45) †,‡	40 (35–50)*,‡	45 (40–55) *,†	<0.001
Medications					
ACEI	286 (31.5)	82 (25.9)‡	137 (32.9)	67 (37.9)*	0.016
ARB	142 (15.6)	45 (14.2)	72 (17.3)	25 (14.1)	0.437
Aldactone	117 (12.9)	20 (6.3)†,‡	51 (12.3)*,‡	46 (26.0)*,†	<0.001
β-Blockers	374 (41.1)	116 (36.7)‡	171 (41.1)	87 (49.2)*	0.027
Calcium channel blockers	185 (20.4)	59 (18.7)	93 (22.4)	33 (18.6)	0.387
Digoxin	269 (29.6)	80 (25.3)‡	113 (27.2)‡	76 (42.9)*,†	<0.001
Statin	373 (41.0)	82 (25.9)†,‡	213 (51.2)*	78 (44.1)*	<0.001
Warfarin	417 (45.9)	115 (36.4)†,‡	198 (47.6)*,‡	104 (58.8)*,†	<0.001
Cardiac surgery risk-stratification models					
EuroScore II	2.42 (1.33–4.50)	1.73 (1.01–2.85)†,‡	2.49 (1.53–4.72)*,‡	4.25 (2.77–8.82)*,†	<0.001
STS Score	1.49 (0.87–2.76)	1.12 (0.63–1.80)†,‡	1.63 (1.02–2.75)*,‡	3.02 (1.39–5.40)*,†	<0.001
Valvular surgery details					
Aortic valve replacement	460 (50.7)	164 (51.9)	214 (51.4)	82 (46.6)	0.482
Mitral valve procedure	554 (61.0)	192 (61.0)	245 (58.9)	117 (66.1)	0.258
Mitral valve replacement	295 (32.5)	97 (30.7)	138 (33.2)	60 (33.9)	0.701
Mitral valve repair	259 (28.6)	95 (30.2)	107 (25.7)	57 (32.6)	0.181
Tricuspid annuloplasty	319 (35.2)	77 (24.4)†,‡	151 (36.3)*,‡	91 (52.0)*,†	<0.001
Concomitant CABG	107 (11.8)	18 (5.7)†,‡	59 (14.2)*	30 (17.1)*	<0.001
Emergency operation	20 (2.2)	3 (0.9)	10 (2.4)	7 (4.0)	0.086
Inotropic support	198 (21.8)	55 (17.4)	100 (24.0)	43 (24.3)	0.065
Operative complications					
Major bleeding events	11 (1.2)	2 (0.6)	6 (1.4)	3 (1.7)	0.493
Stroke	4 (0.4)	3 (0.9)	0 (0.0)	1 (0.6)	0.152

Values are expressed as median (interquartile range) or number (percentage). *P* value by Kruskal–Wallis H test for non-normally distributed continuous variables. *P* value by χ^2 test for categorical variables (Bonferroni correction: *$P<0.05$ vs normal [normal hepatorenal function and well-nourished]; †$P<0.05$ vs mild [hepatorenal dysfunction or malnutrition]; ‡$P<0.05$ vs severe [hepatorenal dysfunction and malnutrition]). ACEI indicates angiotensin-converting enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; ARB, angiotensin II receptor blockers; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; CONUT, controlling nutritional status; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; MELD-XI, modified model for end-stage liver disease excluding international normalized ratio; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; and TR, tricuspid regurgitation.

P<0.001) and CONUT score (0.78 and 0.07, *P*<0.001) to EuroSCORE II. Notably, adding CONUT to a combined model of EuroSCORE II and MELD-XI or MELD-XI to EuroSCORE II and CONUT provided incremental prognostic value (χ^2 increased by 48.1 and 68.9, respectively, *P*<0.001 for both) and significant reclassification improvement (0.77 [95% CI, 0.57–0.96]; 0.45 [95% CI, 0.25–0.66], *P*<0.001 for both). Similar results were observed when STS score replaced EuroSCORE II in the model (Figure 2). Sensitivity analysis replacing the CONUT score with serum albumin did not yield similar incremental value, although significant reclassification improvement was seen in the STS score model (Table S8). The inclusion of MELD-XI and CONUT scores improved calibration of the EuroSCORE II and STS score models (Tables S9A and S9B).

Dynamic Changes of Hepatorenal Function and Nutrition at 1-Year Follow-up

At 1 year after surgery, 707 patients underwent laboratory examination (median interval, 14.5 months [interquartile range, 13–18 months]). The primary and secondary cohorts had similar clinical characteristics (Table S10).

At 1-year follow-up post valvular surgery, 15% of patients had concomitant hepatorenal dysfunction and malnutrition (severe), 41% of patients had either condition (mild), and 43% had neither condition (normal hepatorenal function and nutrition). While hepatorenal function and nutrition deteriorated in 105 (15%) patients after valvular surgery, they remained static in 454 (64%) and had improved in 148 (21%). ΔMELD-XI was correlated with New York Heart Association class III/IV and ΔCONUT score (Table S11A) and was

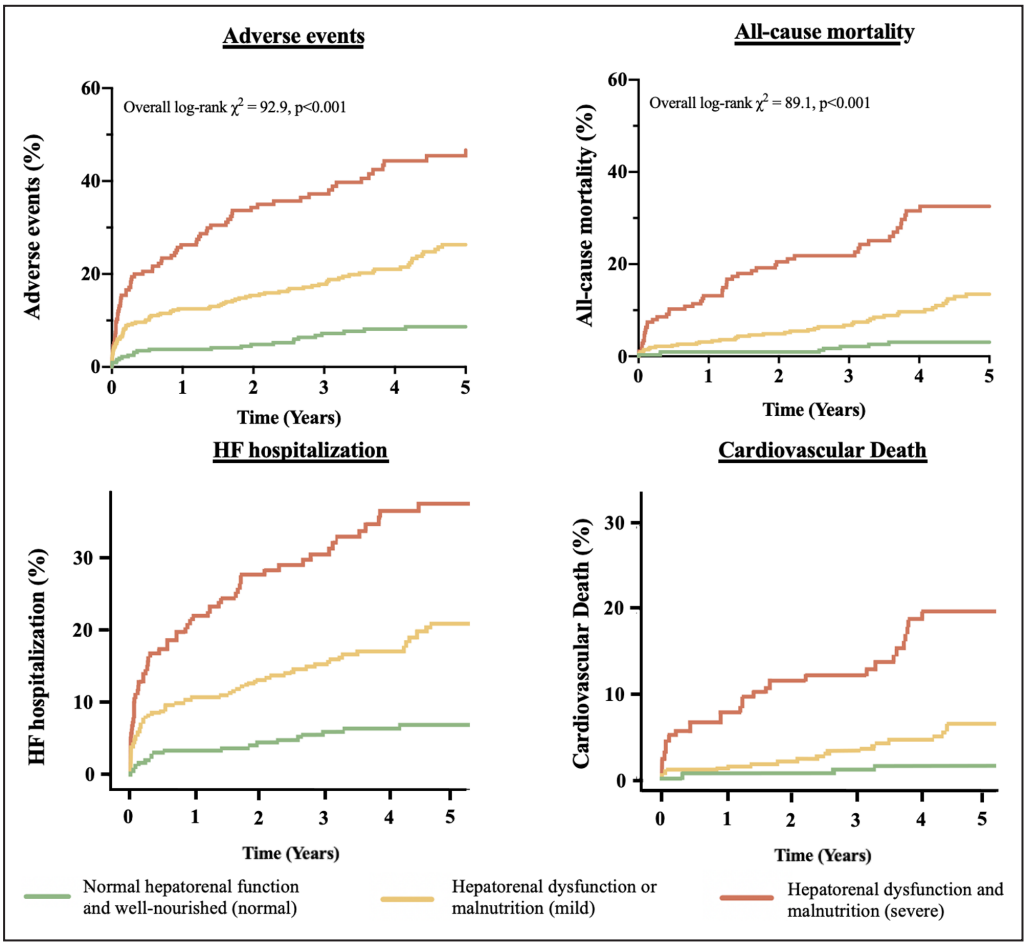


Figure 1. Cumulative incidence curves for all-cause mortality, adverse events, heart failure hospitalization, and cardiovascular death by baseline hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT).
CONUT indicates Controlling Nutritional Status score; and MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio.

significantly associated with mortality (HR, 1.09 [95% CI, 1.02–1.18], *P*=0.020), cardiovascular death (SHR, 1.14 [95% CI, 1.05–1.24], *P*=0.003), HF hospitalization (SHR, 1.10 [95% CI, 1.03–1.17], *P*=0.003), and adverse events (HR, 1.08 [95% CI, 1.03–1.14], *P*=0.001). Similarly, ΔCONUT was associated with EuroSCORE II and ΔMELD-XI (Table S11B) and was a significant predictor of mortality (HR, 1.20 [95% CI, 1.01–1.43], *P*=0.040), HF hospitalization (SHR, 1.23 [95% CI, 1.06–1.42], *P*=0.006), and adverse events (HR, 1.18 [95% CI, 1.02–1.35], *P*=0.020).

Concomitant hepatorenal dysfunction and malnutrition (severe) was evident in 108 (15%) patients following surgery, of whom it was newly developed in 44 (41%). Risk factors for their presence were LV mass, significant TR, EuroSCORE II, and baseline MELD-XI and CONUT scores (Table S11C). Patients with persistent hepatorenal dysfunction and malnutrition following valvular surgery had worse survival (log-rank χ^2 65.2, *P*<0.001) and adverse outcomes (log-rank χ^2 90.4, *P*<0.001) compared with those with preserved hepatorenal function and/or nutrition (Figure 3). Notably, concomitant hepatorenal dysfunction and malnutrition (severe) exhibited a higher risk of mortality (HR, 4.35 [95% CI, [1.91–9.94], *P*<0.001), cardiovascular death (SHR, 10.74 [95% CI, 3.51–32.81], *P*<0.001), HF hospitalization (SHR,5.27 [95% CI, 3.02–9.19], *P*<0.001), and adverse events (HR, 3.61 [95% CI, 1.99–6.55], *P*<0.001).

DISCUSSION

Based on a comprehensive analysis of clinical, echocardiographic, and laboratory data of a large cohort of patients undergoing valvular surgery, we report the following results: (1) hepatorenal dysfunction and malnutrition were prevalent and often coexisted in VHD; (2) hepatorenal dysfunction and malnutrition, correlated with echocardiographic indices of cardiac structure

Table 2. Cox Proportional Hazards Analyses of Baseline Hepatorenal function (MELD-XI) and Nutritional Status (CONUT) for Predicting All-Cause Mortality

	Overall population					
	Univariate analysis		Multivariate analysis (EuroSCORE II model)		Multivariate analysis (STS score model)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographic and anthropometric characteristics						
Age, y	1.06 (1.04–1.08)	<0.001				
Male	1.09 (0.74–1.61)	0.667				
Body mass index, kg/m^2	1.02 (0.97–1.08)	0.398				
NYHA Class III/IV	1.73 (0.96–3.09)	0.067				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	2.01 (1.36–2.97)	<0.001	1.82 (1.13–2.93)	0.014		
Diabetes	3.16 (2.12–4.70)	<0.001				
Smoking	0.86 (0.52–1.44)	0.575				
Dyslipidemia	2.05 (1.38–3.06)	<0.001	1.62 (1.02–2.57)	0.042	1.79 (1.15–2.78)	0.010
Prior myocardial infarction	2.03 (0.98–4.17)	0.055				
Prior stroke	2.32 (1.39–3.86)	0.001	1.61 (0.93–2.78)	0.088	1.70 (0.95–3.06)	0.074
Atrial fibrillation	1.33 (0.89–1.98)	0.159				
Heart failure	1.47 (1.00–2.18)	0.052				
Laboratory examination						
Hemoglobin, g/dL	0.66 (0.60–0.73)	<0.001				
eGFR, mL/min per 1.73 m^2	0.97 (0.96–0.98)	<0.001				
Total bilirubin, mg/dL	1.42 (1.15–1.74)	<0.001				
Total cholesterol, mg/dL	0.984 (0.978–0.990)	<0.001				
Albumin, mg/dL	0.38 (0.24–0.60)	<0.001				
Valvular heart disease and echocardiographic variables						
MS ≥ moderate	0.86 (0.52–1.43)	0.566				
MR ≥ moderate	0.46 (0.30–0.71)	<0.001	0.50 (0.29–0.88)	0.015		
AS ≥ moderate	1.42 (0.94–2.15)	0.1				
AR ≥ moderate	0.91 (0.58–1.44)	0.701				
TR ≥ moderate	2.28 (1.53–3.39)	<0.001	2.38 (1.40–4.04)	0.002		
Chronic Rheumatic Heart Disease	1.35 (0.89–2.04)	0.157				
LV mass, g	1.001 (0.999–1.003)	0.221				
LVEF, %	0.98 (0.96–1.00)	0.019				
PASP, mm Hg	1.01 (0.99–1.02)	0.370				
Medications						
ACEI	1.48 (0.99–2.20)	0.056				
ARB	0.96 (0.55–1.66)	0.876				
β-Blockers	0.79 (0.53–1.19)	0.259				
Calcium channel blockers	1.04 (0.64–1.68)	0.876				
Digoxin	1.44 (0.97–2.16)	0.074				
Statin	1.44 (0.97–2.13)	0.067				
Warfarin	1.49 (1.00–2.20)	0.048	1.15 (0.68–1.95)	0.600	1.47 (0.91–2.36)	0.113
Valvular surgery details						
Aortic valve replacement	1.63 (1.09–2.44)	0.017	1.30 (0.81–2.10)	0.281	1.36 (0.77–2.41)	0.288
Mitral valve procedure	0.56 (0.38–0.83)	0.004	0.67 (0.39–1.15)	0.149	0.47 (0.27–0.84)	0.010
Mitral valve replacement	0.75 (0.48–1.17)	0.198				
Mitral valve repair	0.64 (0.39–1.03)	0.065				

(*Continued*)

Table 2. Continued

	Overall population					
	Univariate analysis		Multivariate analysis (EuroSCORE II model)		Multivariate analysis (STS score model)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tricuspid annuloplasty	1.36 (0.92–2.02)	0.126				
Concomitant CABG	1.28 (0.74–2.22)	0.376				
Cardiac surgery risk-stratification models						
EuroScore II	1.06 (1.05–1.08)	<0.001	1.03 (1.01–1.06)	0.006		
STS Score	1.28 (1.20–1.36)	<0.001			1.16 (1.07–1.25)	<0.001
Combined evaluation of hepatorenal function and nutritional status						
Normal (Normal hepatorenal function and well–nourished)	1.00		1.00		1.00	
Mild (Hepatorenal dysfunction or malnutrition)	4.28 (2.01–9.11)	<0.001	3.17 (1.40–7.17)	0.006	2.93 (1.35–6.38)	0.007
Severe (Hepatorenal dysfunction and malnutrition)	13.86 (6.58–29.23)	<0.001	9.30 (4.09–21.16)	<0.001	8.07 (3.63–17.95)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitors; AR, aortic regurgitation; ARB, angiotensin II receptor blockers; AS, aortic stenosis; CABG, coronary artery bypass grafting; CONUT, controlling nutritional status; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; MELD-XI, modified model for end-stage liver disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; and TR, tricuspid regurgitation.

and function, were associated with excess HF and mortality, with a greater step-up in event risk for concomitant hepatorenal dysfunction and malnutrition (severe) than for either phenotype alone; (3) MELD-XI and CONUT scores provided independent and incremental value for risk-stratification over EuroSCORE II and STS score; and (4) deterioration of hepatorenal function (ΔMELD-XI) and nutritional status (ΔCONUT), along with their persistent dysfunction 1 year following surgery, conferred worse long-term prognosis.

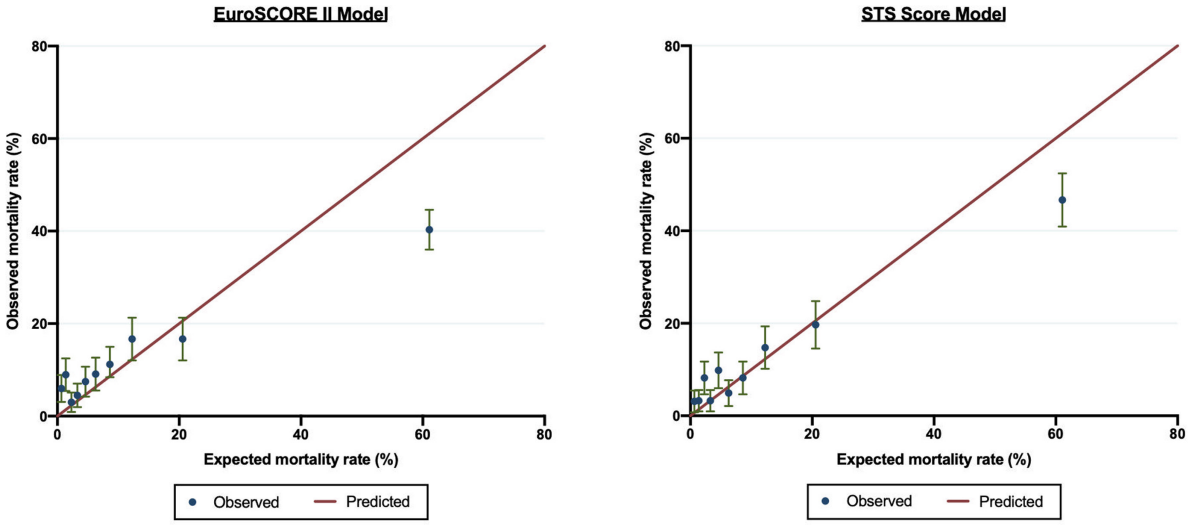
Prevalence and Interaction of Hepatorenal Dysfunction and Malnutrition in VHD

VHD not only adversely affects the myocardium but also is frequently associated with extracardiac pathophysiological consequences. Previous studies[10,12–14] have shown a substantial, albeit variable, prevalence of hepatorenal dysfunction (18%–45%) and malnutrition (42%–94%) in selected valvular procedures. Our study complements existing literature to demonstrate a high prevalence of hepatorenal dysfunction (24%) and malnutrition (61%) in a large and prospectively recruited valvular surgery cohort, and importantly highlights that these 2 conditions often occurred concomitantly (19%). Collectively, these results confirm the close interaction between the cardiovascular system and other organ systems and negate the notion that VHD is a single-organ disease.

There is a complex pathophysiological interaction between the heart and other organ systems. From a pathophysiological point of view, hepatorenal dysfunction develops from venous congestion associated with elevated right-sided filling pressures,[20] whereas malnutrition results from systemic inflammation common to LV dysfunction[21] and pulmonary arterial hypertension,[22] a notion supported by our observations of a lower left ventricular ejection fraction, higher pulmonary artery systolic pressure, and more prevalent TR in patients with hepatorenal dysfunction or malnutrition. Despite potential links between hepatorenal function and nutrition via protein metabolism,[23] they are likely parallel manifestations that represent different downstream sequelae of VHD (Figure 4). The progressive increase in LV mass, pulmonary artery systolic pressure, and significant TR concordant with worsening hepatorenal function and nutrition further implies that their concomitant dysfunction represents an advanced stage of underlying VHD (more severe disease, longer duration, and late surgical referral) where forward and backward failures are key pathophysiologies in their development.

Prognostic Role of Hepatorenal Function and Nutritional Status in Patients Undergoing Valvular Surgery

Although extracardiac organ systems may be considered a receptacle for valvular hemodynamics, evidence is mounting that end-organ damage is not merely a passive bystander but also aggravates excess mortality and morbidity in VHD, even after successful intervention.[24] In this context, hepatorenal dysfunction and malnutrition have emerged as meaningful



Model	C-statistics	cNRI	IDI	Model	C-statistics	cNRI	IDI
EuroSCORE II	0.73	Ref.	Ref.	STS Score	0.72	Ref.	Ref.
EuroSCORE II + CONUT	0.78 (p = 0.026)	0.78 (p < 0.001)	0.07 (p < 0.001)	STS Score + CONUT	0.78 (p = 0.006)	0.72 (p < 0.001)	0.05 (p < 0.001)
EuroSCORE II + MELD-XI	0.77 (p = 0.035)	0.58 (p < 0.001)	0.07 (p < 0.001)	STS Score + MELD-XI	0.76 (p = 0.041)	0.42 (p < 0.001)	0.04 (p = 0.006)
EuroSCORE II + MELD-XI + CONUT	0.80 (p=0.046)	0.77 (p < 0.001)	0.04 (p < 0.001)	STS Score + MELD-XI + CONUT	0.79 (p = 0.030)	0.66 (p < 0.001)	0.03 (p = 0.002)

Figure 2. Discrimination and calibration of MELD-XI and CONUT scores when added to EuroSCORE II and STS score for predicting all-cause mortality.
cNRI indicates continuous net reclassification improvement; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; IDI, integrated discrimination improvement; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; and STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

prognosticators in valvular surgery, although current data[10,12–14] are limited to subpopulations with short follow-up. The present study extends these observations for the first time to a large Asian VHD population and distinctly demonstrates a stepwise increase in the risk of 4 clinically relevant end points across a worsening spectrum of hepatorenal and nutritional phenotypes, independent of EuroSCORE II and STS Score. While putative mechanisms warrant clarification, their combined role in prognostication may be attributed to metabolic derangements, physical deconditioning, and poor wound healing characteristic of hepatorenal dysfunction and malnutrition,[8,25] with the latter being the most common cause of secondary immunologic dysfunction.[26] Their concomitant dysfunction may also lead to an increased vulnerability to small and/or acute stresses[27] that conceivably predispose patients to an escalated adverse outcome during major triggers such as valvular surgery. Accordingly, the combined assessment of hepatorenal function and nutritional status may identify individuals at high risk of HF and death and provide integral prognostic value beyond those captured by EuroSCORE II and STS score alone.

Furthermore, because of their interactions with the cardiovascular system, hepatorenal function and nutritional status do not remain static, and their postoperative assessment may thus inform the clinical course beyond that of baseline evaluation alone. Egbe et al[11] showed an association between temporal deterioration of hepatorenal function and transplant-free survival in patients with Ebstein anomaly, while Gonzalez Ferreiro et al[28] found that patients remaining at nutritional risk after transcatheter aortic valve implantation exhibited an increased risk of mortality and HF hospitalization. Extending these findings, our study demonstrates that concomitant hepatorenal dysfunction and malnutrition persisted in a substantial proportion (15%) of patients undergoing valvular surgery. They had a poorer prognosis and thus they must be closely monitored during postoperative surveillance.

Clinical Implications

Conventional risk-scoring systems, particularly EuroSCORE II and STS score, have been widely used for long-term risk stratification of patients undergoing valvular surgery.[3,4] Although these risk-scoring systems

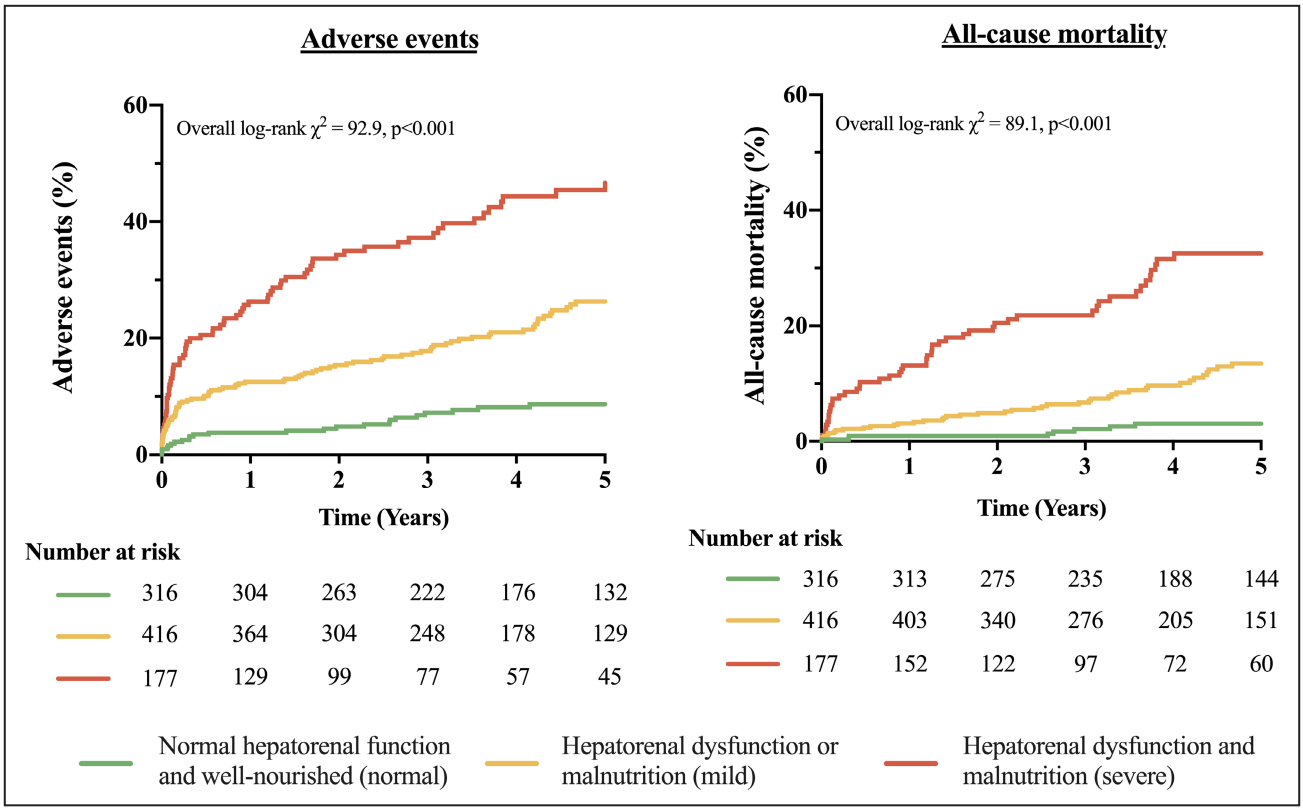


Figure 3. Kaplan–Meier curves for all-cause mortality and adverse events by postoperative hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT).
CONUT indicates Controlling Nutritional Status score; and MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio.

provide good discriminatory power for perioperative mortality, they may serve only as initial estimates of long-term prognosis that is nonetheless central to the lifelong management of patients with VHD. In line with previous studies,[5,29] our results showed that EuroSCORE II (area under the curve: 0.73) and STS score (area under the curve: 0.72) demonstrated only modest accuracy in predicting long-term outcomes, an issue magnified by their tendency to underestimate mortality in high-risk populations that will likely encompass increasingly comorbid patients with multiple valvular lesions.[5,6] In an attempt to optimize risk prediction in VHD, adjunctive measures such as exercise testing[30] and biomarker profiling[31] have been evaluated. These parameters, although prognostically meaningful, are costly and technical, and pose tremendous challenges to their clinical application. The incremental and discriminative prognostic value of MELD-XI and CONUT scores, comprising simple and objective parameters obtained during routine assessment, thus offers an attractive alternative to aid conventional risk-scoring systems. Moreover, their prognostic capacity even in specific valvular procedures and VHD origins provides compelling and generalizable evidence to support their use in the routine clinical setting. Beyond preoperative evaluation, MELD-XI and CONUT scores at longitudinal follow-up offer additional prognostic information that supports continual monitoring of these phenotypes postoperatively. As such, our study provides robust evidence to support an extracardiac workup in addition to EuroSCORE II and STS score for both pre- and postoperative clinical assessment. Accordingly, adopting a multiparametric approach can identify high-risk surgical candidates with a dual burden of cardiac and extracardiac manifestations, who may instead opt for transcatheter valvular interventions as a low-risk alternative. Still, the applicability of MELD and CONUT scores in transcatheter valvular therapies requires further study.

Study Limitations

This was a single-center, retrospective study and was thus subject to limitations inherent to this type of study design. The association between hepatorenal function, malnutrition, and adverse events could have been influenced by potential confounders, although extensive adjustments were made in multiple regression models. Our study evaluated hepatorenal function and nutritional status reflected by MELD-XI and CONUT scores only and did not compare their prognostic value with either liver or kidney imaging data or more complex

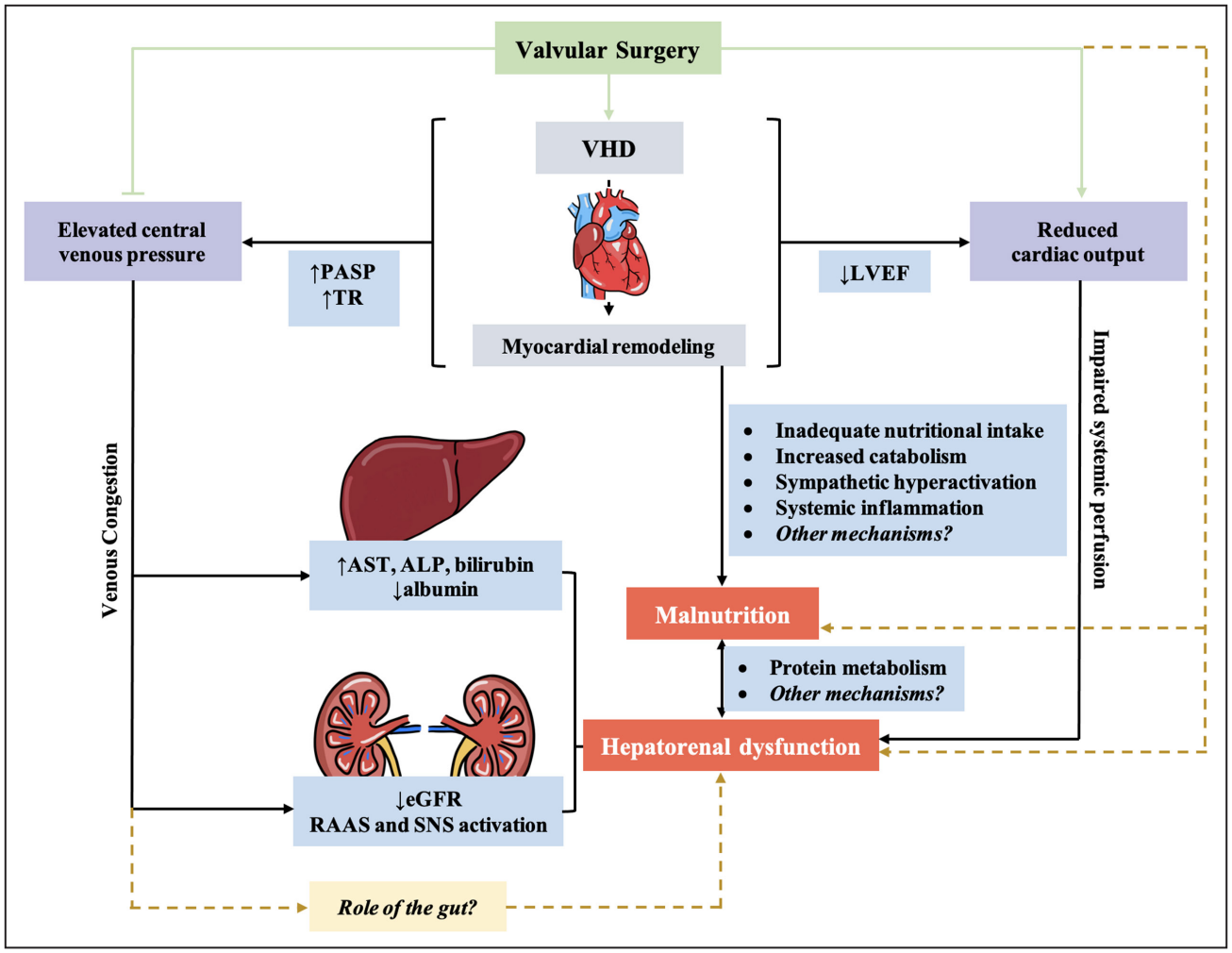


Figure 4. Mechanistic overview of the development of extracardiac sequelae (hepatorenal dysfunction and malnutrition) in valvular heart disease.
ALP indicates alkaline phosphatase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; and VHD, valvular heart disease.

comprehensive nutritional assessments. Nonetheless, MELD-XI and CONUT scores have been well validated[32,33] and showed strong correlation with clinical outcomes.[11–14,19] Patients in the current study were Asians, with a large proportion having chronic rheumatic heart disease. Confirmatory studies in other ethnic groups and degenerative valvular pathologies are warranted, although subgroup analysis demonstrating their sustained prognostic capacity in patients with non–chronic rheumatic heart disease seems to support their utility in various causes of VHD.

CONCLUSIONS

In a large cohort of patients undergoing valvular surgery, we demonstrated that hepatorenal dysfunction and malnutrition, as either isolated or combined phenotypes, are frequent and are associated with cardiac remodeling. Concomitant hepatorenal dysfunction and malnutrition at baseline, and their temporal deterioration at follow-up, have a powerful, independent, and incremental link to excess mortality and worsening HF. Importantly, hepatorenal and nutritional assessment improves the prognostic and discriminatory power of existing valvular surgery risk-scoring systems. These results highlight the prognostic importance of extracardiac organ-system involvement in VHD and have major implications for optimizing risk-stratification in patients undergoing valvular surgery.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients included and excluded from the study

Characteristics	Patients included in the study (n=909)	Patients excluded from the study (n=171)	P value
Demographic and anthropometric characteristics			
Age, years	63 (57-69)	64 (50-72)	0.647
Male	431 (47.4)	91 (53.2)	0.320
Height, cm	159 (153-166)	164 (157-170)	0.002
Weight, kg	58 (50-67)	61 (52-67)	0.717
Body mass index, kg/m^2	23.0 (20.6-25.6)	22.6 (20.3-24.7)	0.103
NYHA Class III/IV	69 (7.6)	10 (5.8)	0.139
Cardiovascular risk factors and cardiovascular disease			
Hypertension	290 (31.9)	53 (31.0)	0.973
Diabetes Mellitus	165 (18.2)	24 (14.0)	0.194
Dyslipidemia	231 (25.4)	30 (17.5)	0.013
Smoking	178 (19.6)	37 (21.6)	0.808
Prior myocardial infarction	37 (4.1)	5 (2.9)	0.404
Prior stroke	82 (9.1)	15 (8.8)	0.867
Heart failure	393 (43.2)	58 (33.9)	0.032
Atrial fibrillation	487 (53.6)	71 (41.5)	0.011
Comorbidities			

Chronic obstructive pulmonary disease	52 (5.7)	7 (4.1)	0.479
Cancer	52 (5.7)	16 (9.4)	0.020
Laboratory examination			
Hemoglobin, g/dL	12.9 (11.6-14.0)	12.9 (11.3-14.1)	0.955
White cell count, x 10^9/L	5.9 (4.9-7.0)	8.3 (5.7-10.6)	<0.001
Platelet count, x 10^9/L	189 (157-227)	284 (191-356)	<0.001
Creatinine, mg/dL	0.92 (0.78-1.14)	–	–
eGFR, ml/min/1.73m^2	75.9 (60.9-90.1)	–	–
AST, U/L	27 (22-35)	–	–
ALT, U/L	21 (16-29)	–	–
ALP, U/L	71 (58-90)	–	–
Total bilirubin, mg/dL	0.53 (0.75-1.14)	–	–
Total cholesterol, mg/dL	159 (134-188)	–	–
Albumin, g/dL	4.2 (4.0-4.4)	–	–
Valvular heart disease and echocardiographic variables			
MS ≥ moderate	229 (25.2)	14 (8.2)	<0.001
MR ≥ moderate	411 (45.2)	112 (62.6)	0.071
AS ≥ moderate	322 (35.4)	33 (19.3)	<0.001
AR ≥ moderate	231 (25.4)	39 (39.2)	0.054
TR ≥ moderate	365 (40.2)	94 (54.9)	0.219

Chronic Rheumatic Heart Disease	259 (28.5)	35 (20.5)	0.052
LVEF, %	60 (55-60)	60 (55-60)	0.548
PASP, mmHg	40 (35-50)	45 (30-75)	0.019
Medications			
ACEI	286 (31.5)	37 (21.6)	0.009
ARB	142 (15.6)	24 (14.0)	0.679
Aldactone	117 (12.9)	23 (13.5)	0.977
Beta blockers	374 (41.1)	63 (36.8)	0.499
Calcium channel blockers	185 (20.4)	27 (15.8)	0.161
Digoxin	269 (29.6)	37 (21.6)	0.155
Statin	373 (41.0)	48 (28.1)	<0.001
Warfarin	417 (45.9)	58 (33.9)	0.005
Cardiac surgery risk-stratification models			
EuroScore II	2.42 (1.33-4.50)	1.68 (1.04-2.78)	<0.001
STS Score	1.49 (0.87-2.76)	0.91 (0.43-1.81)	<0.001
Valvular surgery details			
Aortic valve replacement	460 (50.7)	66 (38.6)	0.209
Mitral valve procedure	554 (61.0)	120 (70.2)	0.398
Mitral valve replacement	295 (32.5)	45 (26.3)	0.584
Mitral valve repair	259 (28.6)	75 (43.9)	0.021

Tricuspid annuloplasty	319 (35.2)	44 (25.7)	0.108
Concomitant CABG	107 (11.8)	14 (8.2)	0.287

Values are expressed as median (interquartile range) or number (percentage). P value by Mann-Whitney U test for non-normally distributed continuous variables; P value by χ^2 test for categorical variables.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S2A. Univariate and multivariate logistic regression models showing predictors of baseline concomitant hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT) (severe) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis (EuroSCORE II model)**		**Multivariate analysis (STS Score model)**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics						
Age, years	1.04 (1.02-1.06)	<0.001				
Male	1.92 (1.38-2.70)	<0.001				
Body mass index, kg/m^2	0.96 (0.92-1.01)	0.087				
NYHA functional class III/IV	2.96 (1.75-4.92)	<0.001				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	1.35 (0.95-1.90)	0.087				
Diabetes Mellitus	2.55 (1.74-3.71)	<0.001				
Smoking	1.36 (0.91-2.01)	0.122				
Dyslipidemia	1.08 (0.74-1.55)	0.698				
Prior myocardial infarction	1.56 (0.71-3.19)	0.240				
Prior stroke	1.84 (1.09-3.02)	0.019	1.33 (0.69-2.47)	0.378	1.67 (0.86-3.21)	0.131
Atrial fibrillation	2.23 (1.58-3.18)	<0.001	1.10 (0.67-1.83)	0.714	1.15 (0.70-1.89)	0.585
Heart failure	2.45 (1.76-3.45)	<0.001	1.43 (0.93-2.21)	0.108	1.42 (0.91-2.23)	0.123

Valvular heart disease and echocardiographic variables						
MS ≥ moderate	0.83 (0.55-1.24)	0.379				
MR ≥ moderate	1.40 (1.01-1.96)	0.045	1.15 (0.73-1.81)	0.548		
AS ≥ moderate	0.78 (0.54-1.12)	0.188				
AR ≥ moderate	0.86 (0.58-1.26)	0.450				
TR ≥ moderate	3.12 (2.22-4.40)	<0.001	1.93 (1.17-3.21)	0.010		
LV Mass, g	1.004 (1.002-1.005)	<0.001	1.005 (1.003-1.008)	<0.001	1.008 (1.005-1.010)	<0.001
LVEF, %	0.97 (0.95-0.98)	<0.001				
PASP, mmHg	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.04)	0.005	1.03 (1.01-1.04)	<0.001
Cardiac surgery risk-stratification models						
EuroSCORE II	1.16 (1.11-1.21)	<0.001	1.17 (1.11-1.24)	<0.001		
STS Score	1.45 (1.33-1.57)	<0.001			1.39 (1.26-1.53)	<0.001

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OR, odds ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S2B. Competing Risk Analysis of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting heart failure hospitalization

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Combined evaluation of hepatorenal function and nutritional status			
Normal (Normal hepatorenal function and well-nourished)	1.00	1.00	1.00
Mild (Hepatorenal dysfunction or malnutrition)	3.08 (1.78-5.35)	2.08 (1.23-3.52)	1.87 (1.08-3.24)
Severe (Hepatorenal dysfunction and malnutrition)	5.77 (3.26-10.23)	3.09 (1.73-5.50)	2.95 (1.59-5.47)

*Adjusted for atrial fibrillation, heart failure, significant tricuspid regurgitation, pulmonary artery systolic pressure, and EuroSCORE II ($P<0.05$ on univariate analysis).

†Adjusted for atrial fibrillation, heart failure, pulmonary artery systolic pressure, and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S2C. Competing Risk Analysis of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting cardiovascular death

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Combined evaluation of hepatorenal function and nutritional status			
Normal (Normal hepatorenal function and well-nourished)	1.00	1.00	1.00
Mild (Hepatorenal dysfunction or malnutrition)	3.97 (1.36-11.6)	3.29 (1.14-9.52)	3.66 (1.24-10.82)
Severe (Hepatorenal dysfunction and malnutrition)	14.70 (5.17-41.7)	9.29 (3.09-27.99)	10.52 (3.49-31.74)

*Adjusted for hypertension, significant tricuspid regurgitation, and EuroSCORE II ($P<0.05$ on univariate analysis).

†Adjusted for hypertension and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S2D. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting adverse events

	Overall Population					
	Univariate analysis		**Multivariate analysis (EuroSCORE II Model)**		**Multivariate analysis (STS Score Model)**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Demographic and anthropometric characteristics						
Age, years	1.05 (1.04-1.07)	<0.001				
Male	1.06 (0.79-1.40)	0.713				
Body mass index, kg/m^2	1.02 (0.98-1.06)	0.428				
NYHA Class III/IV	1.69 (1.09-2.64)	0.020				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	1.52 (1.14-2.04)	0.005	1.61 (1.10-2.36)	0.013		
Diabetes Mellitus	2.41 (1.78-3.27)	<0.001				
Smoking	1.16 (0.82-1.64)	0.391				
Dyslipidemia	1.49 (1.10-2.02)	0.009	1.02 (0.69-1.51)	0.926	1.05 (0.72-1.54)	0.802
Prior myocardial infarction	2.16 (1.27-3.65)	0.004				
Prior stroke	1.91 (1.28-2.86)	0.002	1.33 (0.84-2.11)	0.217	1.39 (0.86-2.26)	0.177
Atrial fibrillation	1.63 (1.22-2.20)	0.001	1.01 (0.63-1.62)	0.957	1.19 (0.72-1.95)	0.497

Heart failure	2.45 (1.82-3.29)	<0.001	2.23 (1.55-3.20)	<0.001		
Laboratory examination						
Hemoglobin, g/dL	0.73 (0.68-0.79)	<0.001				
eGFR, ml/min/1.73m^2	0.974 (0.969-0.980)	<0.001				
Total bilirubin, mg/dL	1.32 (1.13-1.55)	<0.001				
Total cholesterol, mg/dL	0.987 (0.983-0.991)	<0.001				
Albumin, mg/dL	0.40 (0.29-0.56)	<0.001				
Valvular heart disease and echocardiographic variables						
MS ≥ moderate	1.12 (0.80-1.57)	0.519				
MR ≥ moderate	0.74 (0.55-0.99)	0.042	0.51 (0.36-0.73)	<0.001		
AS ≥ moderate	1.12 (0.83-1.53)	0.456				
AR ≥ moderate	0.80 (0.57-1.13)	0.199				
TR ≥ moderate	2.01 (1.51-2.67)	<0.001	1.44 (0.89-2.33)	0.138		
Chronic Rheumatic Heart Disease	1.39 (1.03-1.88)	0.031	1.15 (0.78-1.69)	0.474	0.96 (0.63-1.44)	0.829
LV Mass, g	1.001 (0.999-1.002)	0.328				
LVEF, %	0.97 (0.96-0.99)	<0.001				
PASP, mmHg	1.02 (1.01-1.02)	0.003	1.00 (0.99-1.01)	0.461	1.00 (0.99-1.01)	0.913
Medications						
ACEI	1.62 (1.21-2.16)	0.001	1.40 (0.99-1.97)	0.057	1.78 (1.26-2.51)	0.001

ARB	1.04 (0.70-1.53)	0.848				
Beta blockers	0.95 (0.71-1.28)	0.748				
Calcium channel blockers	0.97 (0.68-1.39)	0.884				
Digoxin	1.42 (1.06-1.91)	0.019				
Statin	1.27 (0.95-1.69)	0.101				
Warfarin	1.68 (1.26-2.23)	<0.001	1.11 (0.70-1.76)	0.645	0.96 (0.60-1.54)	0.866
Valvular surgery details						
Aortic valve replacement	1.13 (0.85-1.51)	0.395				
Mitral valve procedure	0.99 (0.74-1.33)	0.958				
Mitral valve replacement	1.10 (0.82-1.48)	0.547				
Mitral valve repair	0.91 (0.65-1.25)	0.527				
Tricuspid annuloplasty	1.66 (1.25-2.21)	<0.001	1.06 (0.67-1.67)	0.797	1.24 (0.84-1.82)	0.282
Concomitant CABG	1.27 (0.85-1.91)	0.248				
Cardiac surgery risk-stratification models						
EuroScore II	1.06 (1.05-1.07)	<0.001	1.04 (1.02-1.06)	<0.001		
STS Score	1.26 (1.20-1.32)	<0.001			1.16 (1.09-1.23)	<0.001

Combined evaluation of hepatorenal function and nutritional status						
Normal (Normal hepatorenal function and well-nourished)	1.00		1.00		1.00	
Mild (Hepatorenal dysfunction or malnutrition)	3.19 (2.03-4.99)	<0.001	2.11 (1.25-3.55)	0.005	1.97 (1.18-3.32)	0.010
Severe (Hepatorenal dysfunction and malnutrition)	7.22 (4.56-11.44)	<0.001	3.55 (2.04-6.16)	<0.001	3.17 (1.80-5.62)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; CI, confidence interval; CONUT, Controlling Nutritional Status score; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S3A. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting all-cause mortality and adverse events in patients undergoing aortic valve replacement (n=460)

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Separate evaluation of hepatorenal function and nutritional status								
Hepatorenal dysfunction								
MELD-XI, continuous	1.14 (1.09-1.19)	<0.001	1.07 (1.03-1.12)	0.002	1.12 (1.07-1.18)	<0.001	1.08 (1.02-1.13)	0.004
MELD-XI, categorical								
Hepatorenal dysfunction (MELD-XI >12.43)	2.96 (1.69- 5.16)	<0.001	2.28 (1.42-3.67)	<0.001	3.16 (1.79-5.59)	<0.001	2.39 (1.43-4.02)	<0.001
Nutritional status								
CONUT, continuous	1.43 (1.24-1.66)	<0.001	1.32 (1.14-1.53)	<0.001	1.46 (1.27-1.68)	<0.001	1.31 (1.13-1.52)	<0.001
CONUT, categorical								
Normal nutrition	Referent		Referent		Referent		Referent	

Mild malnutrition	3.97 (1.76-8.93)	<0.001	2.88 (1.47-5.64)	0.002	4.72 (1.97-11.30)	<0.001	3.10 (1.52-6.34)	0.002
Moderate to severe malnutrition	8.07 (2.98-21.84)	<0.001	5.73 (2.40-13.64)	<0.001	10.37 (3.68-29.26)	<0.001	5.78 (2.34-14.28)	<0.001
Combined evaluation of hepatorenal function and nutritional status								
Normal (Normal hepatorenal function and well-nourished)	Referent		Referent		Referent		Referent	
Mild (Hepatorenal dysfunction or malnutrition)	4.36 (1.68-11.33)	0.003	2.56 (1.25-5.23)	0.010	4.40 (1.68-11.52)	0.003	2.49 (1.20-5.19)	0.014
Severe (Hepatorenal dysfunction and malnutrition)	9.50 (3.49-25.85)	<0.001	4.76 (2.24-10.13)	<0.001	10.57 (3.88-28.85)	<0.001	5.15 (2.35-11.27)	<0.001

*Adjusted for hypertension, heart failure, concomitant mitral valve procedure, concomitant tricuspid annuloplasty, and EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, atrial fibrillation, prior stroke, baseline warfarin therapy, pulmonary artery systolic pressure, concomitant mitral valve procedure, concomitant tricuspid annuloplasty, and EuroSCORE II ($P<0.05$ on univariate analysis).

‡Adjusted for concomitant mitral valve procedure, concomitant tricuspid annuloplasty, and STS Score ($P<0.05$ on univariate analysis).

§Adjusted for atrial fibrillation, prior stroke, baseline warfarin therapy, pulmonary artery systolic pressure, concomitant mitral valve procedure, concomitant tricuspid annuloplasty, and EuroSCORE II ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S3B. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting all-cause mortality and adverse events in patients undergoing mitral valve procedure (mitral valve replacement or mitral valve repair) (n=554)

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Separate evaluation of hepatorenal function and nutritional status								
Hepatorenal dysfunction								
MELD-XI, continuous	1.12 (1.08-1.17)	<0.001	1.06 (1.02-1.10)	0.002	1.11 (1.06-1.16)	<0.001	1.04 (1.00-1.08)	0.034
MELD-XI, categorical								
Hepatorenal dysfunction (MELD-XI >12.43)	4.13 (2.23-7.63)	<0.001	1.85 (1.25-2.74)	0.002	3.85 (2.02-7.32)	<0.001	1.72 (1.14-2.59)	0.012
Nutritional status								
CONUT, continuous	1.61 (1.34-1.93)	<0.001	1.33 (1.18-1.50)	<0.001	1.54 (1.28-1.86)	<0.001	1.30 (1.15-1.47)	<0.001
CONUT, categorical								
Normal nutrition	Referent		Referent		Referent		Referent	

Mild malnutrition	7.16 (2.16-23.70)	0.001	2.13 (1.28-3.52)	0.004	6.75 (2.03-22.45)	0.002	1.94 (1.16-3.26)	0.012
Moderate to severe malnutrition	20.24 (5.55-73.82)	<0.001	5.33 (2.84-9.99)	<0.001	15.34 (4.08-57.60)	<0.001	4.39 (2.30-8.39)	<0.001
Combined evaluation of hepatorenal function and nutritional status								
Normal (Normal hepatorenal function and well-nourished)	Referent		Referent		Referent		Referent	
Mild (Hepatorenal dysfunction or malnutrition)	3.71 (1.06-12.93)	0.040	2.14 (1.22-3.75)	0.008	3.55 (1.01-12.46)	0.048	2.01 (1.14-3.55)	0.016
Severe (Hepatorenal dysfunction and malnutrition)	14.81 (4.37-50.24)	<0.001	3.60 (1.99-6.51)	<0.001	13.17 (3.83-45.29)	<0.001	3.16 (1.71-5.84)	<0.001

*Adjusted for hypertension, concomitant aortic valve replacement, concomitant tricuspid annuloplasty, and EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, dyslipidemia, prior myocardial infarction, concomitant aortic valve replacement, concomitant tricuspid annuloplasty, concomitant coronary artery bypass grafting, and EuroSCORE II (P<0.05 on univariate analysis).

‡Adjusted for concomitant aortic valve replacement, concomitant tricuspid annuloplasty, and STS Score (P<0.05 on univariate analysis).

§Adjusted for dyslipidemia, prior myocardial infarction, concomitant aortic valve replacement, concomitant tricuspid annuloplasty, concomitant coronary artery bypass grafting, and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S3C. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting all-cause mortality and adverse events in valvular heart disease of rheumatic etiology (n=259)

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Separate evaluation of hepatorenal function and nutritional status								
Hepatorenal dysfunction								
MELD-XI, continuous	1.16 (1.09-1.25)	<0.001	1.10 (1.03-1.17)	0.004	1.28 (1.12-1.47)	<0.001	1.12 (1.01-1.24)	0.032
MELD-XI, categorical								
Hepatorenal dysfunction (MELD-XI >12.43)	3.58 (1.82-7.06)	<0.001	1.89 (1.13-3.14)	0.015	3.72 (1.69-8.18)	0.001	1.86 (1.04-3.32)	0.035
Nutritional status								
CONUT, continuous	1.90 (1.50-2.41)	<0.001	1.44 (1.22-1.70)	<0.001	1.93 (1.45-2.56)	<0.001	1.34 (1.10-1.63)	0.003
CONUT, categorical								
Normal nutrition	Referent		Referent		Referent		Referent	

Mild malnutrition	9.70 (2.15-43.84)	0.003	4.87 (2.26-10.48)	<0.001	6.91 (1.60-29.84)	0.010	3.47 (1.60-7.52)	0.002
Moderate to severe malnutrition	32.94 (6.51-166.67)	<0.001	6.77 (2.60-17.64)	<0.001	22.90 (4.33-121.28)	<0.001	4.10 (1.33-12.65)	0.014
Combined evaluation of hepatorenal function and nutritional status								
Normal (Normal hepatorenal function and well-nourished)	Referent		Referent		Referent		Referent	
Mild (Hepatorenal dysfunction or malnutrition)	5.85 (1.30-26.38)	0.022	5.03 (2.16-11.69)	<0.001	4.60 (1.02-20.72)	0.047	3.36 (1.45-7.77)	0.005
Severe (Hepatorenal dysfunction and malnutrition)	15.22 (3.53-65.73)	<0.001	5.99 (2.55-14.07)	<0.001	14.64 (3.20-66.88)	<0.001	4.91 (1.98-12.20)	<0.001

*Adjusted for EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for heart failure, mitral valve replacement, and EuroSCORE II (P<0.05 on univariate analysis).

‡Adjusted for STS Score (P<0.05 on univariate analysis).

§Adjusted for mitral valve replacement and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S3D. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting all-cause mortality and adverse events in valvular heart disease of non-rheumatic etiology (n=650)

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Separate evaluation of hepatorenal function and nutritional status								
Hepatorenal dysfunction								
MELD-XI, continuous	1.13 (1.09-1.17)	<0.001	1.09 (1.05-1.13)	<0.001	1.08 (1.03-1.13)	<0.001	1.04 (1.00-1.08)	0.057
MELD-XI, categorical								
Hepatorenal dysfunction (MELD-XI >12.43)	3.08 (1.81-5.24)	<0.001	2.03 (1.36-3.02)	<0.001	2.38 (1.33-4.24)	0.003	1.80 (1.17-2.78)	0.008
Nutritional status								
CONUT, continuous	1.44 (1.25-1.66)	<0.001	1.33 (1.19-1.48)	<0.001	1.39 (1.20-1.61)	<0.001	1.30 (1.17-1.45)	<0.001
CONUT, categorical								
Normal nutrition	Referent		Referent		Referent		Referent	

Mild malnutrition	2.99 (1.37-6.54)	0.006	1.89 (1.14-3.11)	0.013	3.03 (1.32-6.97)	0.009	1.71 (1.02-2.88)	0.043
Moderate to severe malnutrition	8.47 (3.43-20.93)	<0.001	4.80 (2.64-8.75)	<0.001	6.79 (2.61-17.67)	<0.001	3.95 (2.07-7.55)	<0.001
Combined evaluation of hepatorenal function and nutritional status								
Normal (Normal hepatorenal function and well-nourished)	Referent		Referent		Referent		Referent	
Mild (Hepatorenal dysfunction or malnutrition)	2.88 (1.17-7.10)	0.021	2.13 (1.21-3.76)	0.009	2.69 (1.09-6.67)	0.032	1.97 (1.11-3.50)	0.020
Severe (Hepatorenal dysfunction and malnutrition)	7.88 (3.12-19.95)	<0.001	3.81 (2.08-6.99)	<0.001	5.88 (2.28-15.17)	<0.001	3.13 (1.65-5.97)	<0.001

*Adjusted for hypertension, dyslipidemia, significant tricuspid regurgitation, aortic valve replacement, and EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, dyslipidemia, atrial fibrillation, heart failure, baseline medical therapy (statin and warfarin), type of valvular surgery, and EuroSCORE II (P<0.05 on univariate analysis).

‡Adjusted for dyslipidemia, aortic valve replacement, and STS Score (P<0.05 on univariate analysis).

§Adjusted for dyslipidemia, atrial fibrillation, baseline medical therapy (statin and warfarin), type of valvular surgery, and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S4. Cox proportional hazards analyses of baseline hepatorenal function (MELD-XI) and nutritional status (CONUT) for predicting all-cause mortality and adverse events at least 30 days after valvular surgery (n=892)

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Separate evaluation of hepatorenal function and nutritional status								
Hepatorenal dysfunction								
MELD-XI, continuous	1.15 (1.11-1.19)	<0.001	1.08 (1.04-1.12)	<0.001	1.12 (1.08-1.17)	<0.001	1.06 (1.02-1.10)	0.006
MELD-XI, categorical								
Hepatorenal dysfunction (MELD-XI >12.43)	3.03 (1.90-4.81)	<0.001	1.69 (1.17-2.42)	0.005	2.81 (1.69-4.68)	<0.001	1.51 (1.02-2.24)	0.041
Nutritional status								
CONUT, continuous	1.41 (1.24-1.61)	<0.001	1.29 (1.16-1.42)	<0.001	1.44 (1.27-1.64)	<0.001	1.25 (1.12-1.39)	<0.001
CONUT, categorical								
Normal nutrition	Referent		Referent		Referent		Referent	

Mild malnutrition	3.79 (1.78-8.08)	<0.001	2.05 (1.28-3.26)	0.003	4.47 (2.00-10.00)	<0.001	1.96 (1.21-3.20)	0.007
Moderate to severe malnutrition	8.88 (3.74-21.06)	<0.001	4.51 (2.57-7.91)	<0.001	10.58 (4.19-26.70)	<0.001	3.79 (2.05-7.00)	<0.001
Combined evaluation of hepatorenal function and nutritional status								
Normal (Normal hepatorenal function and well-nourished)	Referent		Referent		Referent		Referent	
Mild (Hepatorenal dysfunction or malnutrition)	2.88 (1.26-6.59)	0.012	2.15 (1.28-3.62)	0.004	3.03 (1.32-6.97)	0.009	1.97 (1.16-3.35)	0.013
Severe (Hepatorenal dysfunction and malnutrition)	8.19 (3.53-18.99)	<0.001	3.26 (1.87-5.68)	<0.001	8.48 (3.60-20.00)	<0.001	2.83 (1.57-5.10)	<0.001

*Adjusted for hypertension, dyslipidemia, prior stroke, significant tricuspid regurgitation, type of valvular surgery, and EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, dyslipidemia, atrial fibrillation, heart failure, prior myocardial infarction, prior stroke, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), significant tricuspid regurgitation, pulmonary artery systolic pressure, type of valvular surgery, and EuroSCORE II ($P<0.05$ on univariate analysis).

‡ Adjusted for dyslipidemia, prior stroke, type of valvular surgery, and STS Score ($P<0.05$ on univariate analysis).

§Adjusted for dyslipidemia, prior myocardial infarction, prior stroke, atrial fibrillation, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), pulmonary artery systolic pressure, type of valvular surgery, and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S5A. Baseline characteristics of the study population according to hepatorenal function (MELD-XI)

Characteristics	Overall (n=909)	Normal hepatorenal function (MELD-XI ≤12.43) (n=693)	Hepatorenal dysfunction (MELD-XI >12.43) (n=216)	P value
Demographic and anthropometric characteristics				
Age, years	63 (57-69)	62 (56-68)	64 (59-70)	<0.001
Male	431 (47.4)	295 (42.6)	136 (63.0)	<0.001
Height, cm	159 (153-166)	159 (153-165)	160 (154-167)	0.158
Weight, kg	58 (50-67)	58 (51-67)	58 (50-68)	0.857
Body mass index, kg/m^2	23.0 (20.6-25.6)	23.2 (20.7-25.7)	22.7 (19.9-25.4)	0.149
NYHA Class III/IV	69 (7.6)	40 (5.8)	29 (13.4)	<0.001
Cardiovascular risk factors and cardiovascular disease				
Hypertension	290 (31.9)	209 (30.2)	81 (37.5)	0.045
Diabetes Mellitus	165 (18.2)	104 (15.0)	64 (28.2)	<0.001
Dyslipidemia	231 (25.4)	171 (24.7)	60 (27.8)	0.371
Smoking	178 (19.6)	123 (17.7)	55 (25.5)	0.014
Prior myocardial infarction	37 (4.1)	24 (3.5)	13 (6.0)	0.114
Prior stroke	82 (9.1)	54 (7.8)	28 (13.1)	0.022
Heart failure	393 (43.2)	260 (37.5)	133 (61.6)	<0.001
Atrial fibrillation	487 (53.6)	343 (49.5)	144 (66.7)	<0.001
Comorbidities				

Chronic obstructive pulmonary disease	52 (5.7)	39 (5.6)	13 (6.0)	0.867
Cancer	52 (5.7)	42 (6.1)	10 (4.6)	0.504
Laboratory examination				
Hemoglobin, g/dL	12.9 (11.6-14)	13.1 (12-14)	11.8 (10.2-13.5)	<0.001
White cell count, x 10^9/L	5.9 (4.9-7.0)	5.9 (4.9-6.8)	6.0 (4.8-7.6)	0.292
Platelet count, x 10^9/L	189 (157-227)	192 (165-228)	177 (134-222)	<0.001
Creatinine, mg/dL	0.92 (0.78-1.14)	0.86 (0.75-1.01)	1.37 (1.12-1.54)	<0.001
eGFR, ml/min/1.73m^2	75.9 (60.9-90.1)	81.5 (69.8-93.5)	51.8 (38.0-62.4)	<0.001
AST, U/L	27 (22-35)	26 (22-33)	30 (25-40)	<0.001
ALT, U/L	21 (16-29)	21 (16-29)	20 (16-27)	0.167
ALP, U/L	71 (58-90)	70 (56-85)	82 (63-113)	<0.001
Total bilirubin, mg/dL	0.75 (0.53-1.14)	0.67 (0.51-0.94)	1.5 (0.76-2.13)	<0.001
Total cholesterol, mg/dL	159 (134-188)	164 (139-193)	142 (120-165)	<0.001
Albumin, g/dL	4.2 (4-4.4)	4.2 (4-4.4)	4 (3.7-4.3)	<0.001
Valvular heart disease and echocardiographic variables				
MS ≥ moderate	229 (25.2)	182 (30.7)	47 (25.7)	0.196
MR ≥ moderate	411 (45.2)	294 (43.0)	17 (54.7)	0.003
AS ≥ moderate	322 (35.4)	254 (40.5)	68 (34.9)	0.179
AR ≥ moderate	231 (25.4)	183 (27.6)	48 (22.6)	0.179
TR ≥ moderate	365 (40.2)	242 (34.9)	123 (57.2)	<0.001

Chronic Rheumatic Heart Disease	259 (28.5)	200 (28.9)	59 (27.3)	0.724
LV Mass, g	224 (176-294)	218 (170-283)	248 (194-314)	<0.001
LVEF, %	60 (55-60)	60 (55-60)	55 (50-60)	<0.001
Preserved, ≥50%	763 (84.3)	599 (86.6)	164 (77.0)	0.001
Mid-range, 40% - 49%	57 (6.3)	45 (6.5)	12 (5.6)	0.748
Reduced, <40%	55 (6.1)	29 (4.2)	26 (12.2)	<0.001
PASP, mmHg	40 (35-50)	40 (35-50)	45 (40-55)	<0.001
Medications				
ACEI	286 (31.5)	204 (29.4)	82 (38.0)	0.019
ARB	142 (15.6)	108 (15.6)	34 (15.7)	1.000
Aldactone	117 (12.9)	67 (9.7)	50 (23.1)	<0.001
Beta blockers	374 (41.1)	264 (38.1)	110 (50.9)	0.001
Calcium channel blockers	185 (20.4)	143 (20.6)	42 (19.4)	0.772
Digoxin	269 (29.6)	183 (26.4)	86 (39.8)	<0.001
Statin	373 (41)	274 (39.5)	99 (45.8)	0.113
Warfarin	417 (45.9)	300 (43.3)	117 (54.2)	0.006
Cardiac surgery risk-stratification models				
EuroScore II	2.4 (1.3-4.5)	2.1 (1.2-3.8)	4.2 (2.5-7.8)	<0.001
STS Score	1.5 (0.9-2.8)	1.4 (0.8-2.3)	2.5 (1.2-4.8)	<0.001
Valvular surgery details				

Aortic valve replacement	460 (50.7)	363 (52.4)	97 (45.1)	0.072
Mitral valve procedure	554 (61)	410 (59.2)	144 (66.7)	0.055
Mitral valve replacement	295 (32.5)	226 (32.6)	69 (31.9)	0.868
Mitral valve repair	259 (28.6)	184 (26.6)	75 (35.0)	0.019
Tricuspid annuloplasty	319 (35.2)	215 (31.0)	104 (48.6)	<0.001
Concomitant CABG	107 (11.8)	71 (10.3)	36 (16.8)	0.011

Values are expressed as median (interquartile range) or number (percentage). P value by Mann-Whitney U test for non-normally distributed continuous variables; P value by χ^2 test for categorical variables.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S5B. Univariate and multivariate logistic regression models showing predictors of baseline hepatorenal dysfunction (MELD-XI) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis (EuroSCORE II model)**		**Multivariate analysis (STS Score model)**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics						
Age, years	1.03 (1.01-1.05)	<0.001				
Male	2.29 (1.68-3.15)	<0.001				
Body mass index, kg/m^2	0.97 (0.93-1.01)	0.166				
NYHA functional class III/IV	2.53 (1.52-4.18)	<0.001				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	1.39 (1.01-1.91)	0.044	1.10 (0.69-1.75)	0.674		
Diabetes Mellitus	2.23 (1.55-3.20)	<0.001				
Smoking	1.58 (1.10-2.27)	0.013	2.12 (1.26-3.53)	0.004	2.56 (1.50-4.38)	<0.001
Dyslipidemia	1.17 (0.83-1.65)	0.361				
Prior myocardial infarction	1.79 (0.87-3.52)	0.101	0.98 (0.33-2.75)	0.973	0.80 (0.27-2.28)	0.689
Prior stroke	1.77 (1.08-2.85)	0.021	1.40 (0.74-2.61)	0.297	1.33 (0.66-2.62)	0.422
Atrial fibrillation	2.04 (1.49-2.82)	<0.001	1.27 (0.78-2.09)	0.342	1.31 (0.81-2.15)	0.268
Heart failure	2.67 (1.95-3.66)	<0.001	1.63 (1.06-2.52)	0.026		

Valvular heart disease and echocardiographic variables						
MS ≥ moderate	0.78 (0.53-1.13)	0.195				
MR ≥ moderate	1.60 (1.18-2.18)	0.003	1.97 (1.25-3.13)	0.004		
AS ≥ moderate	0.78 (0.56-1.10)	0.159				
AR ≥ moderate	0.77 (0.53-1.10)	0.155				
TR ≥ moderate	2.49 (1.83-3.41)	<0.001	1.19 (0.72-1.95)	0.503		
LV Mass, g	1.004 (1.002-1.005)	<0.001	1.004 (1.001-1.006)	0.002	1.007 (1.004-1.009)	<0.001
LVEF, %	0.96 (0.95-0.98)	<0.001				
PASP, mmHg	1.03 (1.02-1.04)	<0.001	1.01 (1.00-1.03)	0.071	1.02 (1.01-1.03)	0.007
Cardiac surgery risk-stratification models						
EuroSCORE II	1.14 (1.10-1.19)	<0.001	1.11 (1.06-1.18)	<0.001		
STS Score	1.39 (1.28-1.50)	<0.001			1.26 (1.15-1.40)	<0.001
Nutritional status						
CONUT, continuous	1.76 (1.58-1.97)	<0.001	1.62 (1.41-1.88)	<0.001	1.64 (1.42-1.91)	<0.001

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OR, odds ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S5C. Cox proportional hazards analysis of baseline hepatorenal function (MELD-XI) for predicting all-cause mortality and adverse events

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Hepatorenal function								
MELD-XI, continuous	1.14 (1.10-1.17)	<0.001	1.09 (1.05-1.12)	<0.001	1.11 (1.07-1.16)	<0.001	1.05 (1.01-1.09)	0.010
MELD-XI, categorical								
Normal hepatorenal function	1.00		1.00		1.00		1.00	
Hepatorenal dysfunction (MELD-XI >12.43)	3.35 (2.20-5.12)	<0.001	1.88 (1.32-2.67)	<0.001	2.94 (1.84-4.70)	<0.001	1.70 (1.17-2.48)	0.006

*Adjusted for hypertension, dyslipidemia, prior stroke, baseline warfarin therapy, type of valvular lesion, type of valvular surgery, EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, dyslipidemia, prior stroke, atrial fibrillation, heart failure, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), chronic rheumatic heart disease, type of valvular lesion, tricuspid annuloplasty, pulmonary artery systolic pressure and EuroSCORE II (P<0.05 on univariate analysis).

‡Adjusted for dyslipidemia, prior stroke, baseline warfarin therapy, type of valvular surgery, and STS Score (P<0.05 on univariate analysis).

§Adjusted for dyslipidemia, prior stroke, atrial fibrillation, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), chronic rheumatic heart disease, tricuspid annuloplasty, pulmonary artery systolic pressure, and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S5D. Competing Risk Analysis of baseline hepatorenal function (MELD-XI) for predicting cardiovascular death and heart failure hospitalization

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Hepatorenal function			
MELD-XI, continuous	1.08 (1.06-1.11)	1.06 (1.02-1.10)	1.06 (1.02-1.10)
MELD-XI, categorical			
Normal hepatorenal function	1.00	1.00	1.00
Hepatorenal dysfunction (MELD-XI >12.43)	2.78 (2.02-3.82)	1.65 (1.11-2.45)	1.71 (1.12-2.61)

*Adjusted for atrial fibrillation, heart failure, significant tricuspid regurgitation, pulmonary artery systolic pressure, and EuroSCORE II ($P<0.05$ on univariate analysis).

†Adjusted for atrial fibrillation, heart failure, pulmonary artery systolic pressure, and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S5E. Competing Risk Analysis of baseline hepatorenal function (MELD-XI) for predicting cardiovascular death

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Hepatorenal function			
MELD-XI, continuous	1.12 (1.09-1.16)	1.10 (1.06-1.14)	1.08 (1.03-1.14)
MELD-XI, categorical			
Normal hepatorenal function	1.00	1.00	1.00
Hepatorenal dysfunction (MELD-XI >12.43)	4.53 (2.64-7.76)	3.23 (1.83-5.70)	3.18 (1.71-5.92)

*Adjusted for hypertension, significant tricuspid regurgitation, and EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S6A. Baseline characteristics of the study population according to nutritional status (CONUT)

Characteristics	Overall (n=909)	Normal nutritional status (n=355)	Mild malnutrition (n=480)	Moderate to severe malnutrition (n=74)	P value
Demographic and anthropometric characteristics					
Age, years	63 (57-69)	60 (54-66)†‡	65 (59-70)*	64 (57-71)*	<0.001
Male	431 (47.4)	161 (45.4)	232 (48.3)	38 (51.4)	0.54
Height, cm	159 (153-166)	160 (155-167)	159 (153-165)	158 (153-165)	0.29
Weight, kg	58 (50-67)	61 (53-69)†‡	57 (50-66)*	53 (46-63)*	<0.001
Body mass index, kg/m^2	23 (20.6-25.6)	24 (21-26)†‡	23 (20-26)*	21 (19-25)*	<0.001
NYHA Class III/IV	69 (7.6)	20 (5.6)‡	38 (7.9)	11 (14.9)*	0.022
Cardiovascular risk factors and cardiovascular disease					
Hypertension	290 (31.9)	93 (26.2)†	175 (36.5)*	22 (29.7)	0.01
Diabetes Mellitus	165 (18.2)	33 (9.3)†‡	110 (22.9)*	22 (29.7)*	<0.001
Dyslipidemia	231 (25.4)	77 (21.7)	136 (28.3)	18 (24.3)	0.09
Smoking	178 (19.6)	78 (22.0)	86 (17.9)	14 (18.9)	0.34
Prior myocardial infarction	37 (4.1)	9 (2.5)	25 (5.2)	3 (4.1)	0.16
Prior stroke	82 (9.1)	20 (5.6)‡	47 (9.9)‡	15 (20.3)*†	<0.001
Heart failure	393 (43.2)	139 (39.2)‡	207 (43.1)	47 (63.5)*	<0.001
Atrial fibrillation	487 (53.6)	156 (43.9)†‡	280 (58.3)*	51 (68.9)*	<0.001
Comorbidities					

Chronic obstructive pulmonary disease	52 (5.7)	15 (4.2)	32 (6.7)	5 (6.8)	0.30
Cancer	52 (5.7)	22 (6.2)	28 (5.8)	2 (2.7)	0.49
Laboratory examination					
Hemoglobin, g/dL	12.9 (11.6-14)	13.4 (12.5-14.5)†‡	12.7 (11.5-13.7)*‡	10.6 (9.6-11.8)*†	<0.001
White cell count, x 10^9/L	5.9 (4.9-7.0)	6.1 (5.3-7.0)†‡	5.8 (4.7-7.0)*‡	4.7 (3.8-6.3)*†	<0.001
Platelet count, x 10^9/L	189 (157-227)	201 (174-236)†‡	182 (147-219)*‡	168 (114-203)*†	<0.001
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.8-1.0)†‡	0.9 (0.8-1.2)*‡	1.2 (0.9-1.5)*†	<0.001
eGFR, ml/min/1.73m^2	75.9 (60.9-90.1)	80.8 (69.2-94.0)†‡	74.0 (59.3-89.2)*‡	60.3 (38.0-75.0)*†	<0.001
AST, U/L	27 (22-35)	26 (22-32)†‡	28 (23-36)*	29 (24-43)*	<0.001
ALT, U/L	21 (16-29)	22 (17-30)	20 (16-28)	19.5 (14-27)	0.03
ALP, U/L	71 (58-90)	67 (55-84)†‡	73 (58-90.2)*‡	98 (68.2-134)*†	<0.001
Total bilirubin, mg/dL	0.7 (0.5-1.1)	0.6 (0.5-0.9)†‡	0.8 (0.6-1.2)*‡	1.2 (0.9-2.1)*†	<0.001
Total cholesterol, mg/dL	159 (134-188)	189 (166-210)†‡	143 (125-164)*‡	127 (113-139)*†	<0.001
Albumin, g/dL	4.2 (4-4.4)	4.3 (4-4.5)†‡	4.2 (4-4.4)*‡	3.7 (3.3-4)*†	<0.001
Valvular heart disease and echocardiographic variables					
MS ≥ moderate	229 (25.2)	89 (28.8)	129 (31.9)	11 (17.7)	0.07
MR ≥ moderate	411 (45.2)	174 (49.6)	207 (43.7)	30 (41.1)	0.17
AS ≥ moderate	322 (35.4)	121 (38.1)	180 (41.2)	21 (31.3)	0.27
AR ≥ moderate	231 (25.4)	96 (28.7)	122 (26.0)	13 (18.3)	0.19
TR ≥ moderate	365 (40.2)	91 (25.6)†‡	222 (46.3)*‡	52 (70.3)*†	<0.001

Chronic Rheumatic Heart Disease	259 (28.5)	91 (25.6)	151 (31.5)	17 (23.0)	0.14
LV Mass, g	224 (176-294)	224 (175-291)	225 (175-290)	224 (194-297)	0.38
LVEF, %	60 (55-60)	60 (55-60)‡	60 (55-60)	57.5 (46.2-60)*	0.01
Preserved, ≥50%	763 (84.3)	305 (86.4)‡	403 (84.3)	55 (74.3)*	0.03
Mid-range, 40% - 49%	57 (6.3)	20 (5.7)	33 (6.9)	4 (5.4)	0.73
Reduced, <40%	55 (6.1)	17 (4.8)‡	27 (5.6)‡	11 (14.9)*	0.004
PASP, mmHg	40 (35-50)	40 (30-46)†‡	45 (35-53)*	45 (40-55)*	<0.001
Medications					
ACEI	286 (31.5)	97 (27.3)	164 (34.2)	25 (33.8)	0.10
ARB	142 (15.6)	54 (15.2)	80 (16.7)	8 (10.8)	0.42
Aldactone	117 (12.9)	24 (6.8)†‡	68 (14.2)*‡	25 (33.8)*†	<0.001
Beta blockers	374 (41.1)	139 (39.2)	203 (42.3)	32 (43.2)	0.61
Calcium channel blockers	185 (20.4)	68 (19.2)	105 (21.9)	12 (16.2)	0.41
Digoxin	269 (29.6)	90 (25.4)‡	146 (30.4)‡	33 (44.6)*†	0.004
Statin	373 (41)	103 (29.0)†	245 (51.0)*‡	25 (33.8)†	<0.001
Warfarin	417 (45.9)	128 (36.1)†‡	239 (49.8)*‡	50 (67.6)*†	<0.001
Cardiac surgery risk-stratification models					
EuroScore II	2.4 (1.3-4.5)	1.8 (1.0-3.0)†‡	2.8 (1.7-5.5)*‡	5.9 (3.2-9.5)*†	<0.001
STS Score	1.5 (0.9-2.8)	1.1 (0.6-1.9)†‡	1.8 (1.1-3.2)*‡	3.3 (1.7-5.5)*†	<0.001
Valvular surgery details					

Aortic valve replacement	460 (50.7)	179 (50.4)	252 (52.5)	29 (39.7)	0.13
Mitral valve procedure	554 (61)	219 (61.9)	292 (60.8)	43 (58.1)	0.83
Mitral valve replacement	295 (32.5)	106 (29.9)	168 (35.0)	21 (28.4)	0.22
Mitral valve repair	259 (28.6)	113 (31.9)	124 (25.9)	22 (29.7)	0.16
Tricuspid annuloplasty	319 (35.2)	90 (25.4)†‡	189 (39.5)*‡	40 (54.8)*†	<0.001
Concomitant CABG	107 (11.8)	24 (6.8)†‡	70 (14.6)*	13 (17.8)*	0.001

Values are expressed as median (interquartile range) or number (percentage). P value by Kruskal-Wallis H test for non-normally distributed continuous variables. P value by χ^2 test for categorical variables (Bonferroni correction: *P<0.05 vs normal nutritional status, †P<0.05 vs mild malnutrition [CONUT score of 2 to 4], ‡P<0.05 vs moderate to severe malnutrition [CONUT score of 5-12]).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S6B. Univariate and multivariate logistic regression models showing predictors of baseline malnutrition (CONUT) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis (EuroSCORE II model)**		**Multivariate analysis (STS Score model)**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics						
Age, years	1.06 (1.04-1.07)	<0.001				
Male	1.15 (0.88-1.50)	0.32				
Body mass index, kg/m^2	0.94 (0.91-0.98)	0.002	0.93 (0.89-0.98)	0.010	0.94 (0.89-0.99)	0.021
NYHA functional class III/IV	1.63 (0.96-2.84)	0.08				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	1.55 (1.16-2.09)	0.003	1.92 (1.20-3.13)	0.007		
Diabetes Mellitus	3.05 (2.05-4.65)	<0.001				
Smoking	0.78 (0.56-1.09)	0.147				
Dyslipidemia	1.39 (1.02-1.91)	0.040	1.00 (0.62-1.62)	0.994	1.13 (0.71-1.81)	0.609
Prior myocardial infarction	2.05 (0.99-4.65)	0.066				
Prior stroke	2.13 (1.28-3.67)	0.005	1.70 (0.86-3.53)	0.137	1.77 (0.85-3.89)	0.138
Atrial fibrillation	1.89 (1.45-2.48)	<0.001	0.95 (0.61-1.48)	0.827	0.93 (0.61-1.40)	0.726
Heart failure	1.32 (1.00-1.73)	0.047	0.77 (0.52-1.13)	0.178		

Valvular heart disease and echocardiographic variables						
MS ≥ moderate	1.06 (0.77-1.45)	0.725				
MR ≥ moderate	0.78 (0.59-1.02)	0.067				
AS ≥ moderate	1.08 (0.81-1.44)	0.601				
AR ≥ moderate	0.83 (0.61-1.13)	0.233				
TR ≥ moderate	2.85 (2.14-3.82)	<0.001	2.02 (1.30-3.16)	0.002		
LV Mass, g	1.001 (0.999-1.002)	0.449				
LVEF, %	0.98 (0.97-0.99)	0.008				
PASP, mmHg	1.03 (1.02-1.04)	<0.001	1.01 (1.00-1.02)	0.188	1.01 (1.00-1.03)	0.036
Cardiac surgery risk-stratification models						
EuroSCORE II	1.14 (1.10-1.19)	<0.001	1.15 (1.07-1.25)	<0.001		
STS Score	1.39 (1.28-1.50)	<0.001			1.34 (1.18-1.56)	<0.001
Hepatorenal dysfunction						
eGFR, ml/min/1.73m^2	0.98 (0.97-0.98)	<0.001				
MELD-XI, continuous	1.29 (1.21-1.39)	<0.001	1.23 (1.13-1.37)	<0.001	1.26 (1.14-1.40)	<0.001

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OR, odds ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S6C. Cox proportional hazards analysis of baseline nutritional status (CONUT) for predicting all-cause mortality and adverse events

	Multivariate analysis							
	EuroSCORE II model				**STS Score model**			
	All-cause mortality*		Adverse events†		All-cause mortality‡		Adverse events§	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Nutritional status								
CONUT, continuous	1.41 (1.25-1.58)	<0.001	1.28 (1.16-1.42)	<0.001	1.43 (1.27-1.62)	<0.001	1.30 (1.17-1.45)	<0.001
CONUT, categorical								
Normal nutrition	1.00		1.00		1.00		1.00	
Mild malnutrition	3.81 (1.87-7.75)	<0.001	2.06 (1.29-3.28)	0.002	3.88 (1.89-7.93)	<0.001	1.99 (1.24-3.20)	0.004
Moderate to severe malnutrition	7.97 (3.58-17.77)	<0.001	4.17 (2.35-7.41)	<0.001	7.95 (3.42-18.48)	<0.001	3.89 (2.14-7.10)	<0.001

*Adjusted for hypertension, dyslipidemia, prior stroke, baseline warfarin therapy, type of valvular lesion, type of valvular surgery, EuroSCORE II (P<0.05 on univariate analysis).

†Adjusted for hypertension, dyslipidemia, prior stroke, atrial fibrillation, heart failure, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), chronic rheumatic heart disease, type of valvular lesion, tricuspid annuloplasty, pulmonary artery systolic pressure and EuroSCORE II (P<0.05 on univariate analysis).

‡Adjusted for dyslipidemia, prior stroke, baseline warfarin therapy, type of valvular surgery, and STS Score (P<0.05 on univariate analysis).

§Adjusted for dyslipidemia, prior stroke, atrial fibrillation, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), chronic rheumatic heart disease, tricuspid annuloplasty, pulmonary artery systolic pressure, and STS Score (P<0.05 on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HR, hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S6D. Competing Risk Analysis of baseline nutritional status (CONUT) for predicting heart failure hospitalization

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Nutritional Status			
CONUT, continuous	1.44 (1.32-1.56)	1.29 (1.16-1.42)	1.26 (1.12-1.41)
CONUT, categorical			
Normal nutrition	1.00	1.00	1.00
Mild malnutrition	2.46 (1.53-3.95)	2.09 (1.30-3.37)	1.96 (1.18-3.24)
Moderate to severe malnutrition	5.92 (3.39-10.36)	4.00 (2.23-7.17)	3.25 (1.64-6.43)

*Adjusted for atrial fibrillation, heart failure, significant tricuspid regurgitation, pulmonary artery systolic pressure, and EuroSCORE II ($P<0.05$ on univariate analysis).

†Adjusted for atrial fibrillation, heart failure, pulmonary artery systolic pressure, and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S6E. Competing Risk Analysis of baseline nutritional status (CONUT) for predicting cardiovascular death

	Unadjusted	**EuroSCORE II model***	**STS Score model†**
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Nutritional Status			
CONUT, continuous	1.62 (1.44-1.83)	1.53 (1.35-1.74)	1.61 (1.41-1.84)
CONUT, categorical			
Normal nutrition	1.00	1.00	1.00
Mild malnutrition	5.21 (2.03-13.4)	3.94 (1.55-10.02)	3.97 (1.50-10.49)
Moderate to severe malnutrition	16.42 (5.98-45.1)	10.31 (3.73-28.51)	11.21 (3.78-33.26)

*Adjusted for hypertension, significant tricuspid regurgitation, and EuroSCORE II ($P<0.05$ on univariate analysis).

†Adjusted for hypertension and STS Score ($P<0.05$ on univariate analysis).

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SHR, subdistribution hazard ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S7. Calibration of the Cox proportional hazards models for predicting all-cause mortality and adverse events

Outcome	**EuroSCORE II model**		**STS Score model**	
	Wald Chi-square	P value	Wald Chi-square	P value
All-cause mortality	2.22	0.137	1.93	0.165
Adverse events	4.90	0.180	1.36	0.506

Abbreviations: EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S8. Incremental prognostic and discriminatory value of adding serum albumin to EuroSCORE II and STS Score

Models	**C-statistics**	**P value**	**cNRI**	**P value**	**IDI**	**P value**
Death						
EuroSCORE II	0.73	<0.001	Ref		Ref	
EuroSCORE II + Albumin	0.72	0.602	0.21	0.053	0.01	0.088
STS Score	0.72	<0.001	Ref		Ref	
STS Score + Albumin	0.74	0.209	0.25	0.027	0.01	0.032

Abbreviations: cNRI, continuous net reclassification improvement; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; IDI, integrated discrimination improvement; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S9A. Changes in Calibration of the Cox proportional hazards models for predicting all-cause mortality with inclusion of the MELD-XI and CONUT scores

	EuroSCORE II*	**EuroSCORE II + MELD-XI**	**EuroSCORE II + CONUT**	**EuroSCORE II + MELD-XI + CONUT**	**STS Score†**	**STS Score + MELD-XI**	**STS Score + CONUT**	**STS Score + MELD-XI + CONUT**
Likelihood Ratio Test	-463	-445	-449	-437	-391	-382	-379	-370
P value‡	–	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001
AIC	943	911	918	896	794	777	771	755
BIC	965	935	942	922	807	793	786	773

*Fully adjusted model comprising baseline comorbidities (hypertension, dyslipidemia, prior stroke), type of valvular lesion (significant mitral regurgitation, significant tricuspid regurgitation), baseline warfarin therapy, type of valvular procedure (aortic valve replacement and mitral valve procedure), and EuroSCORE II as in Table 2.

†Fully adjusted model comprising baseline comorbidities (dyslipidemia, prior stroke), type of valvular lesion (significant mitral regurgitation, significant tricuspid regurgitation), baseline warfarin therapy, type of valvular procedure (aortic valve replacement and mitral valve procedure), and STS Score as in Table 2.

‡Compared to EuroSCORE II / STS Score model.

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S9B. Changes in Calibration of the Cox proportional hazards models for predicting adverse events with inclusion of the MELD-XI and CONUT scores

	EuroSCORE II*	**EuroSCORE II + MELD-XI**	**EuroSCORE II + CONUT**	**EuroSCORE II + MELD-XI + CONUT**	**STS Score†**	**STS Score + MELD-XI**	**STS Score + CONUT**	**STS Score + MELD-XI + CONUT**
Likelihood Ratio Test	-905	-897	-893	-889	-789	-786	-779	-778
P value‡	–	<0.001	<0.001	<0.001	–	0.028	<0.001	<0.001
AIC	1836	1821	1815	1807	1596	1593	1596	1579
BIC	1875	1864	1857	1853	1622	1622	1621	1610

*Fully adjusted model comprising baseline comorbidities (hypertension, dyslipidemia, prior stroke, atrial fibrillation, heart failure), type of valvular lesion (significant mitral regurgitation, significant tricuspid regurgitation), chronic rheumatic heart disease, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), tricuspid annuloplasty and EuroSCORE II as in Table S2D.

†Fully adjusted model comprising baseline comorbidities (dyslipidemia, prior stroke, atrial fibrillation), chronic rheumatic heart disease, baseline medical therapy (angiotensin-converting enzyme inhibitors, warfarin), tricuspid annuloplasty and STS Score as in Table S2D.

‡Compared to EuroSCORE II / STS Score model.

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score.

Table S10. Baseline characteristics of the secondary cohort compared with the rest of the study population

Characteristics	Patients included in the secondary cohort (n=707)	Patients not included in the secondary cohort (n=202)	P value
Demographic and anthropometric characteristics			
Age, years	63 (57-69)	62 (55-69)	0.221
Male	339 (47.9)	92 (45.5)	0.576
Height, cm	160 (153-166)	158 (153-166)	0.257
Weight, kg	59 (51-67)	56 (50-66)	0.052
Body mass index, kg/m^2	23.4 (20.6-25.9)	22.1 (20.3-24.8)	0.010
NYHA Class III/IV	51 (7.2)	18 (8.9)	0.451
Cardiovascular risk factors and cardiovascular disease			
Hypertension	236 (33.4)	54 (26.7)	0.087
Diabetes Mellitus	136 (19.2)	29 (14.4)	0.121
Dyslipidemia	190 (26.9)	41 (20.3)	0.067
Smoking	138 (19.5)	40 (19.8)	1.000
Prior myocardial infarction	29 (4.1)	8 (4.0)	1.000
Prior stroke	62 (8.8)	20 (10.0)	0.676
Heart failure	321 (45.4)	72 (35.6)	0.016
Atrial fibrillation	377 (53.3)	110 (54.4)	0.811
Comorbidities			

Chronic obstructive pulmonary disease	38 (5.4)	14 (6.9)	0.492
Cancer	34 (4.8)	18 (8.9)	0.038
Laboratory examination			
Hemoglobin, g/dL	12.9 (11.8-14.1)	12.5 (11.0-13.7)	0.005
White cell count, x 10^9/L	5.9 (4.8-7.1)	5.9 (4.9-6.7)	0.551
Platelet count, x 10^9/L	189 (159-226)	188 (152-234)	0.942
Creatinine, mg/dL	0.93 (0.78-1.12)	0.89 (0.77-1.21)	0.833
eGFR, ml/min/1.73m^2	75.5 (61.5-89.5)	78.3 (57.2-93.7)	0.687
AST, U/L	27 (23-34)	28 (22-37)	0.655
ALT, U/L	21 (16-29)	20 (16-28)	0.436
ALP, U/L	71 (58-89)	73 (59-100)	0.039
Total bilirubin, mg/dL	0.75 (0.53-1.10)	0.73 (0.53-1.23)	0.345
Total cholesterol, mg/dL	160 (134-189)	154 (132-185)	0.341
Albumin, g/dL	4.2 (4-4.4)	4.2 (3.9-4.4)	0.463
Valvular heart disease and echocardiographic variables			
MS ≥ moderate	176 (29.6)	53 (29.3)	1.000
MR ≥ moderate	325 (46.6)	86 (43.0)	0.377
AS ≥ moderate	255 (40.3)	67 (35.4)	0.236
AR ≥ moderate	184 (27.2)	47 (23.6)	0.317
TR ≥ moderate	272 (38.5)	93 (46.0)	0.061

Chronic Rheumatic Heart Disease	197 (27.9)	62 (30.7)	0.486
LV Mass, g	225 (176-294)	218 (176-293)	0.444
LVEF, %	60 (55-60)	60 (51-60)	0.949
Preserved, ≥50%	591 (84.1)	172 (85.1)	0.743
Mid-range, 40% - 49%	45 (6.4)	12 (5.9)	0.871
Reduced, <40%	43 (6.1)	12 (5.9)	1.000
PASP, mmHg	40 (35-50)	45 (35-51)	0.125
Medications			
ACEI	227 (32.1)	59 (29.2)	0.441
ARB	110 (15.6)	32 (15.8)	1.000
Aldactone	80 (11.3)	37 (18.3)	0.012
Beta blockers	290 (41.0)	84 (41.6)	0.935
Calcium channel blockers	146 (20.7)	39 (19.3)	0.694
Digoxin	209 (29.6)	60 (29.7)	1.000
Statin	304 (43.0)	69 (34.2)	0.028
Warfarin	322 (45.5)	95 (47.0)	0.749
Cardiac surgery risk-stratification models			
EuroScore II	2.43 (1.38-4.39)	2.41 (1.20-4.80)	0.955
STS Score	1.49 (0.88-2.60)	1.58 (0.77-3.48)	0.584
Valvular surgery details			

Aortic valve replacement	363 (51.4)	97 (48.0)	0.425
Mitral valve procedure	434 (61.5)	120 (59.4)	0.624
Mitral valve replacement	227 (32.1)	68 (33.7)	0.733
Mitral valve repair	207 (29.4)	52 (25.7)	0.332
Tricuspid annuloplasty	242 (34.3)	77 (38.1)	0.358
Concomitant CABG	92 (13.0)	15 (7.5)	0.035

Values are expressed as median (interquartile range) or number (percentage). P value by Mann-Whitney U test for non-normally distributed continuous variables; P value by χ^2 test for categorical variables.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S11A. Univariate and multivariate linear regression models showing predictors of 1-year change in MELD-XI score (ΔMELD-XI) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics				
Age, years	1.01 (0.99-1.03)	0.188		
Male	0.76 (0.56-1.03)	0.079		
Body mass index, kg/m^2	1.03 (0.99-1.07)	0.199		
NYHA functional class III/IV	0.39 (0.22-0.69)	0.001	0.54 (0.30-0.99)	0.045
Cardiovascular risk factors and cardiovascular disease				
Hypertension	1.58 (1.14-2.20)	0.006	1.23 (0.86-1.74)	0.253
Diabetes Mellitus	1.81 (1.21-2.70)	0.004	1.37 (0.90-2.07)	0.137
Smoking	0.80 (0.54-1.17)	0.249		
Dyslipidemia	1.29 (0.90-1.84)	0.163		
Prior myocardial infarction	2.13 (0.97-4.68)	0.060		
Prior stroke	0.70 (0.41-1.20)	0.195		
Atrial fibrillation	0.61 (0.45-0.83)	0.002	0.74 (0.51-1.07)	0.111
Heart failure	0.67 (0.49-0.91)	0.010	0.78 (0.56-1.10)	0.157
Valvular heart disease and echocardiographic variables				

MS ≥ moderate	0.98 (0.69-1.41)	0.932		
MR ≥ moderate	0.58 (0.43-0.79)	<0.001	0.76 (0.52-1.09)	0.134
AS ≥ moderate	1.62 (1.17-2.23)	0.004	1.24 (0.85-1.81)	0.258
AR ≥ moderate	1.34 (0.93-1.91)	0.112		
TR ≥ moderate	0.56 (0.41-0.77)	<0.001	0.97 (0.66-1.42)	0.871
LV Mass, g	1.000 (0.998-1.002)	0.928		
LVEF, %	1.01 (1.00-1.03)	0.125		
PASP, mmHg	0.99 (0.98-1.00)	0.120		
EuroSCORE II	1.01 (0.98-1.05)	0.479		
STS Score	0.99 (0.91-1.07)	0.790		
Nutritional status				
Baseline CONUT, continuous	0.85 (0.77-0.95)	0.002		
ΔCONUT	0.89 (0.78-1.01)	<0.001	1.22 (1.00-1.37)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate aminotransferase; CABG, coronary artery bypass grafting; CONUT, Controlling Nutritional Status score; ΔCONUT, 1-year change in CONUT score; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S11B. Univariate and multivariate linear regression models showing predictors of 1-year change in CONUT score (ΔCONUT) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics				
Age, years	0.99 (0.98-1.00)	0.182		
Male	1.12 (0.91-1.38)	0.270		
Body mass index, kg/m^2	1.02 (0.99-1.05)	0.138		
NYHA functional class III/IV	0.80 (0.54-1.19)	0.263		
Cardiovascular risk factors and cardiovascular disease				
Hypertension	1.00 (0.80-1.24)	0.974		
Diabetes Mellitus	1.09 (0.84-1.41)	0.515		
Smoking	1.23 (0.95-1.59)	0.114		
Dyslipidemia	0.92 (0.73-1.16)	0.491		
Prior myocardial infarction	1.50 (0.90-2.51)	0.124		
Prior stroke	0.83 (0.58-1.20)	0.319		
Atrial fibrillation	0.91 (0.74-1.11)	0.343		
Heart failure	0.91 (0.74-1.11)	0.344		
Valvular heart disease and echocardiographic variables				

MS ≥ moderate	1.06 (0.83-1.35)	0.627		
MR ≥ moderate	1.12 (0.91-1.38)	0.269		
AS ≥ moderate	1.04 (0.84-1.30)	0.709		
AR ≥ moderate	0.79 (0.62-1.00)	0.049	0.74 (0.57-0.95)	0.019
TR ≥ moderate	0.73 (0.60-0.91)	0.004	0.85 (0.67-1.083)	0.188
LV Mass, g	1.000 (0.998-1.001)	0.480		
LVEF, %	1.01 (1.00-1.02)	0.020		
PASP, mmHg	0.99 (0.98-1.00)	0.008	0.99 (0.99-1.00)	0.103
EuroSCORE II	0.97 (0.95-0.99)	0.009	0.98 (0.95-1.00)	0.041
STS Score	0.97 (0.92-1.03)	0.292		
Hepatorenal function				
Baseline MELD-XI, continuous	0.99 (0.96-1.03)	0.626		
ΔMELD-XI	1.12 (1.07-1.17)	<0.001	1.16 (1.11-1.21)	<0.001

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; ΔMELD-XI, 1-year change in MELD-XI score; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OR, odds ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Table S11C. Univariate and multivariate logistic regression models showing predictors of postoperative hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT) in patients undergoing valvular surgery

	Univariate analysis		**Multivariate analysis (EuroSCORE II model)**		**Multivariate analysis (STS Score model)**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Demographic and anthropometric characteristics						
Age, years	1.06 (1.03-1.08)	<0.001				
Male	2.06 (1.36-3.16)	<0.001				
Body mass index, kg/m^2	1.03 (0.97-1.09)	0.300				
NYHA functional class III/IV	1.79 (0.87-3.46)	0.093				
Cardiovascular risk factors and cardiovascular disease						
Hypertension	1.75 (1.15-2.65)	0.009	1.87 (1.00-3.51)	0.050		
Diabetes Mellitus	3.42 (2.18-5.33)	<0.001				
Smoking	1.30 (0.78-2.09)	0.302				
Dyslipidemia	1.45 (0.92-2.23)	0.101				
Prior myocardial infarction	2.63 (1.11-5.79)	0.020	0.45 (0.07-2.36)	0.372	0.70 (0.11-3.38)	0.673
Prior stroke	1.38 (0.68-2.60)	0.347				
Atrial fibrillation	1.16 (0.77-1.76)	0.475				
Heart failure	1.94 (1.28-2.95)	0.002	1.12 (0.60-2.10)	0.721		

Valvular Heart Disease and Echocardiographic variables						
MS ≥ moderate	0.82 (0.48-1.37)	0.463				
MR ≥ moderate	1.18 (0.78-1.78)	0.441				
AS ≥ moderate	1.05 (0.67-1.62)	0.835				
AR ≥ moderate	0.86 (0.52-1.37)	0.539				
TR ≥ moderate	1.95 (1.29-2.95)	0.002	1.28 (0.65-2.53)	0.481		
LV Mass, g	1.004 (1.002-1.006)	<0.001	1.004 (1.000-1.007)	0.025	1.004 (1.001-1.008)	0.006
LVEF, %	0.97 (0.96-0.99)	0.009				
PASP, mmHg	1.02 (1.01-1.04)	0.005	1.00 (0.98-1.02)	0.663	1.00 (0.98-1.02)	0.984
Cardiac surgery risk-stratification models						
EuroSCORE II	1.13 (1.08-1.19)	<0.001	1.14 (1.07-1.23)	<0.001		
STS Score	1.31 (1.19-1.43)	<0.001			1.12 (0.98-1.29)	0.09
Baseline Hepatorenal function						
MELD-XI, continuous	1.54 (1.42-1.69)	<0.001	1.47 (1.31-1.65)	<0.001	1.43 (1.28-1.61)	<0.001
Baseline Nutritional status						
CONUT, continuous	1.75 (1.53-2.03)	<0.001	1.28 (1.05-1.56)	0.014	1.37 (1.12-1.68)	0.002

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CONUT, Controlling Nutritional Status score; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LV, left ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OR, odds ratio; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.

Figure S1. Study population flowchart for inclusion of patients undergoing valvular surgery

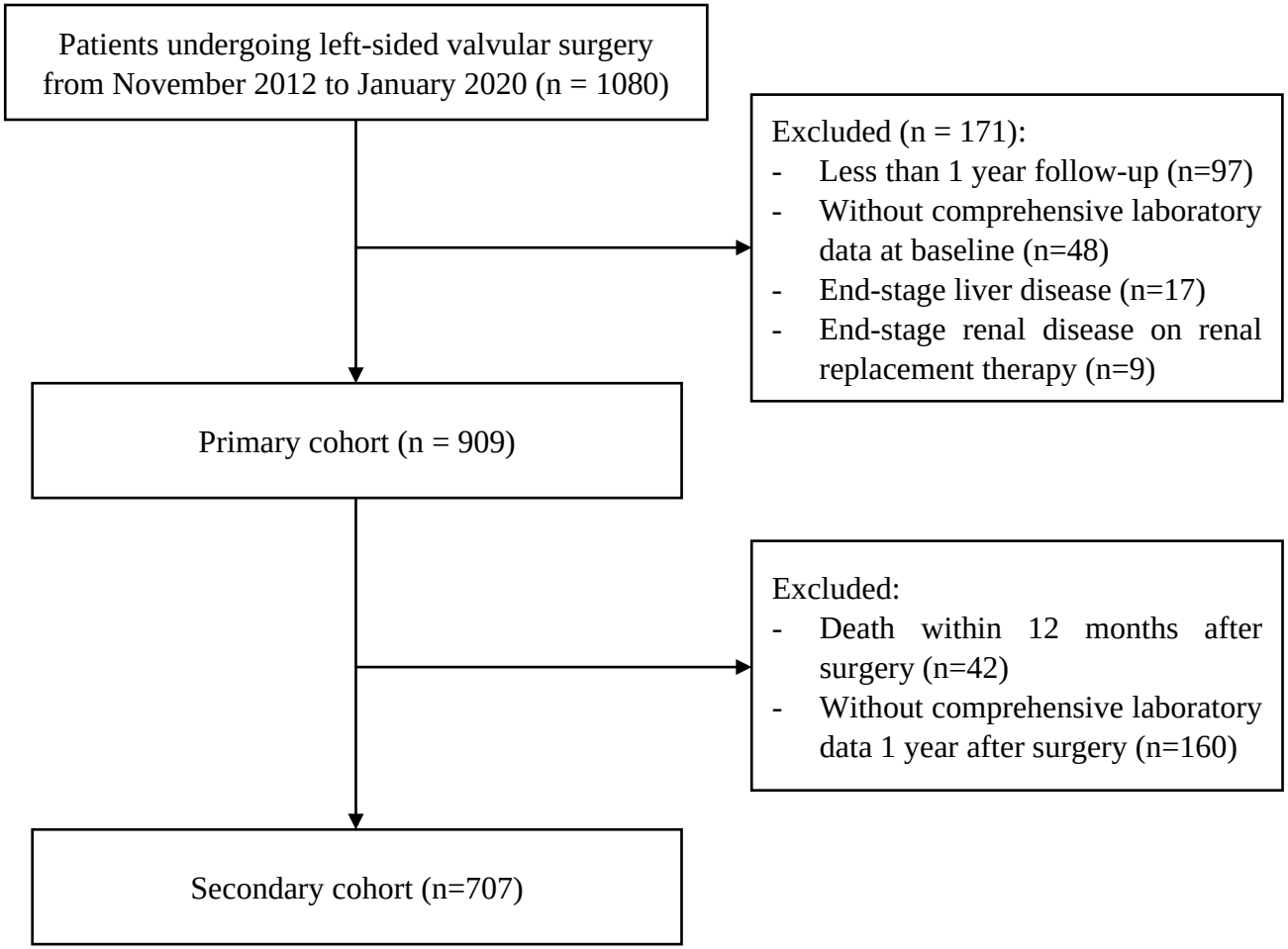
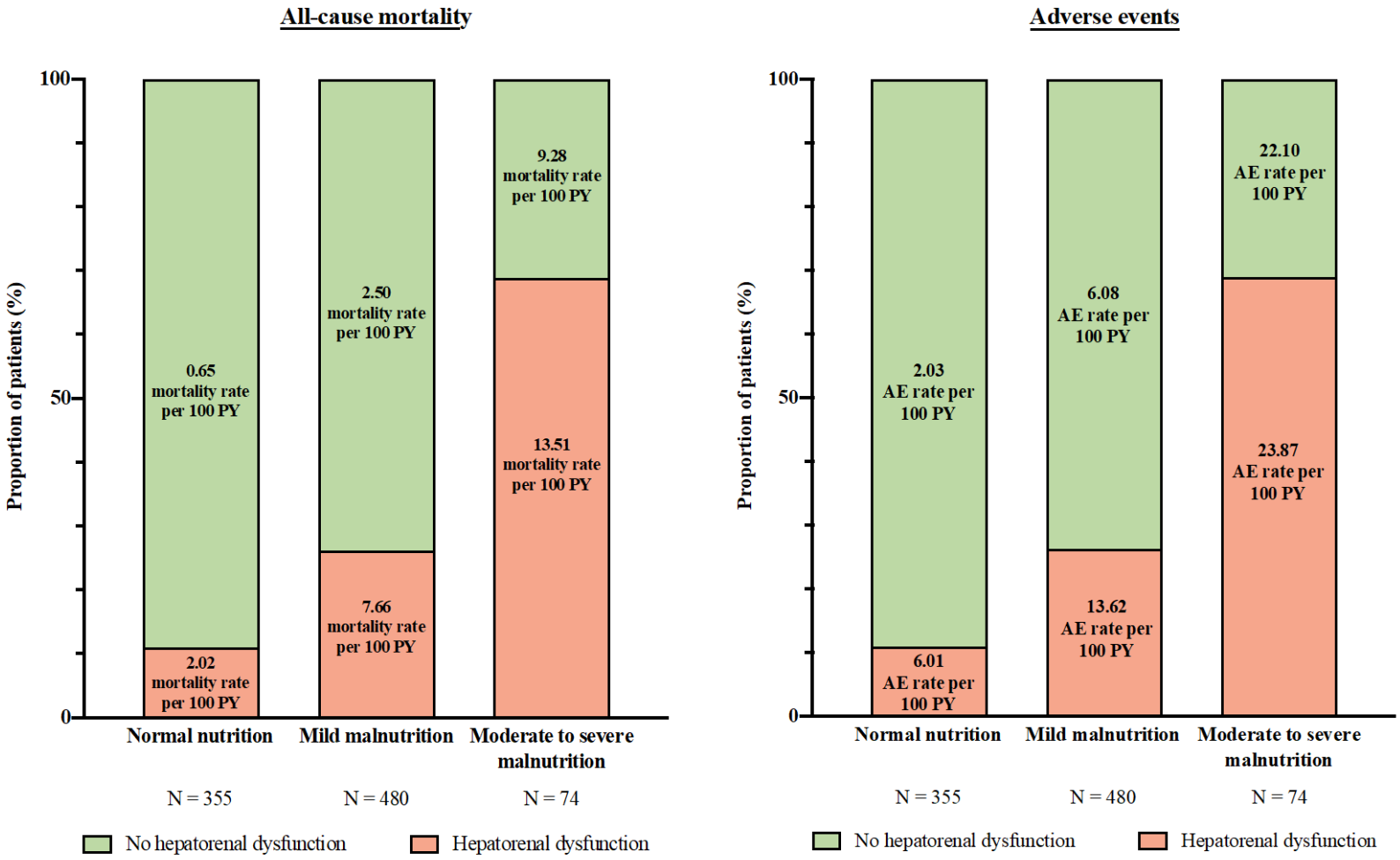


Figure S2. Prevalence and association of hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT) with incidence of all-cause mortality and adverse events



Abbreviations: AE, adverse event; PY, person-years.

Figure S3. Kaplan-Meier curves for all-cause mortality and adverse events by baseline hepatorenal dysfunction (MELD-XI) and malnutrition (CONUT)

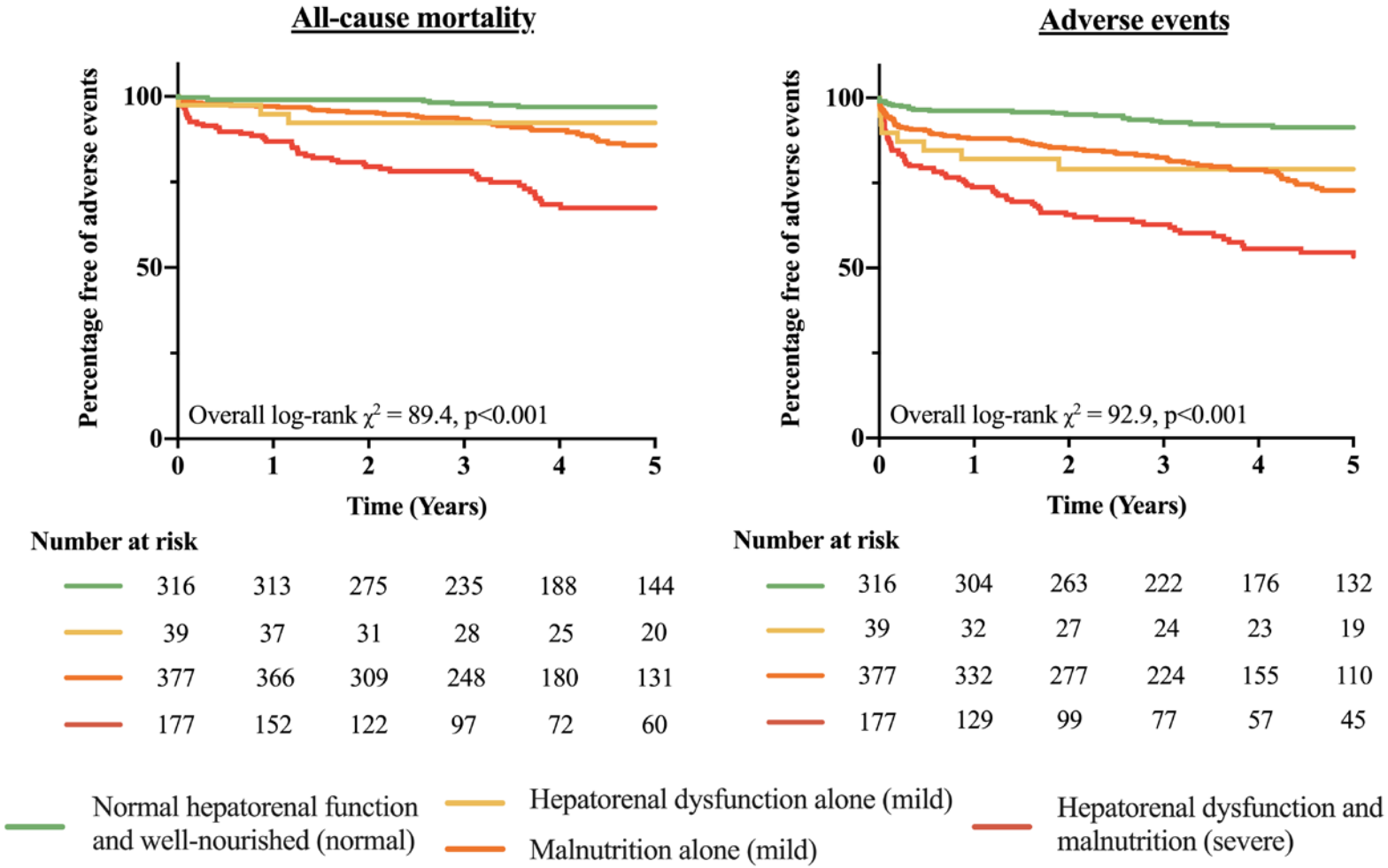
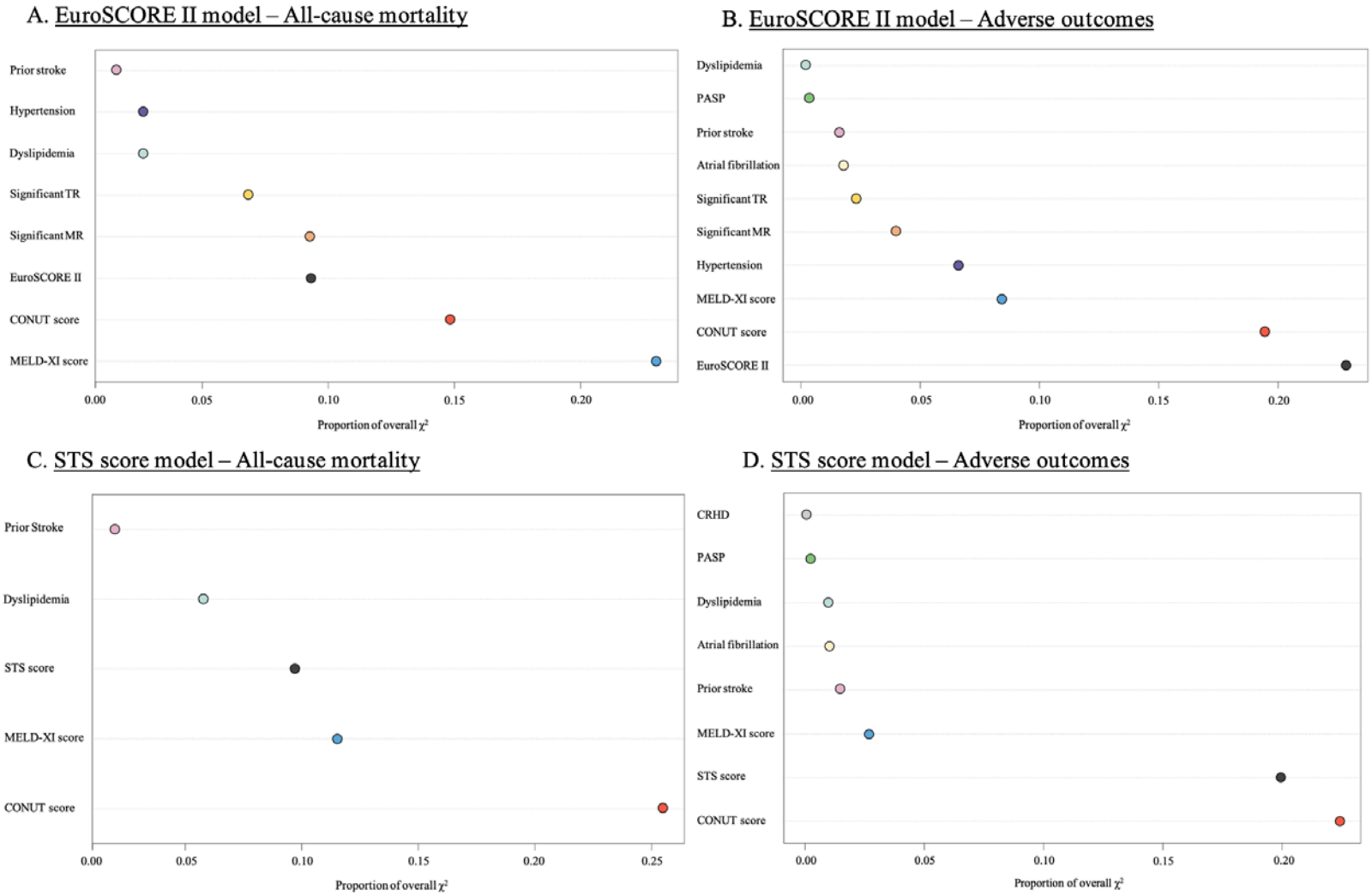
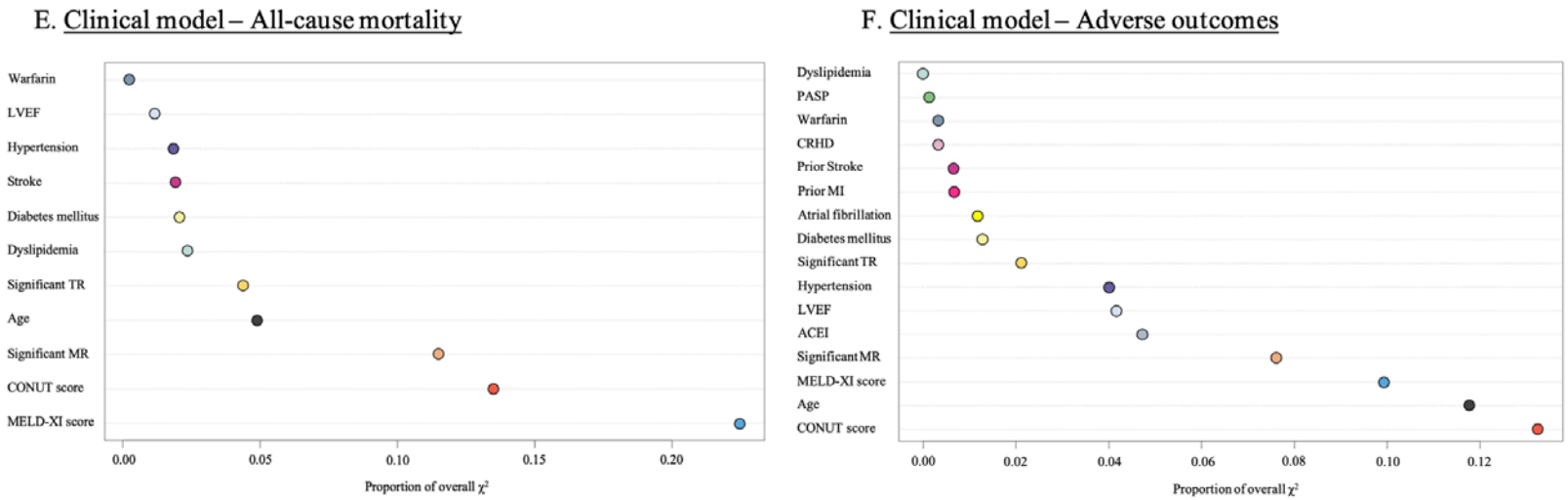


Figure S4. Strength of association of clinical and echocardiographic covariates and risk scores with mortality and adverse outcomes according to the explained log-likelihood (χ^2) for each predictor in patients undergoing valvular surgery





Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; CONUT, Controlling Nutritional Status score; CRHD, chronic rheumatic heart disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF; left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons Predicted Risk of Mortality Score; TR, tricuspid regurgitation.