Supplementary Material

Appendix A: Details of data collection

We retrieved and linked all prespecified medical data during both inpatient and outpatient settings within the observed period from WECODe, namely age, sex, smoking status, alcohol consumption, discharge diagnosis with ICD-10 codes and free text, admission department (Department of Cardiology/other), admission date, discharge date, discharge department and patient status on the discharge; the dates and records of medication prescription (Supplementary Table SI); vital signs (systolic and diastolic blood pressure [BP], and heart rate); laboratory test results (Supplementary Table SII). Supplementary Table SIII summarizes the ICD-10 codes or diagnosis with free text for other comorbidities.

We only evaluated the last hospitalization with a discharge diagnosis of "New York Heart Association class II, III, or IV" if patients were admitted more than once; the admission date was set as the index date for each eligible individual; the baseline window was set as the period of 30 days prior and one day post-index date. We used the record of a given parameter closest to the index date during the baseline window as the baseline value. Especially, the baseline HbA1c was identified as the closest measurement to the index date 90 days before and one day after the index date; The baseline heart rate, systolic BP, diastolic BP, and prescriptions were identified as the first records on or next to the index date.

Supplementary Table SI. Details of prescription information

Medication	Anatomical Therapeutic Chemical (ATC) Classification
Insulin	Insulins and analogs for injection, fast-acting
	Insulins and analogs for injection, intermediate-acting
	Insulins and analogs for injection, intermediate- or long-acting combined with fast-acting
	Insulins and analogs for injection, long-acting
ACEI	ACE inhibitors, plain
	ACE inhibitors and diuretics
	ACE inhibitors and dihydropyridine derivatives
	ACE inhibitors, plain and folic acid and derivatives
	ACE inhibitors, other combinations
ARB	ARB, plain
	ARB and diuretics
	ARB and CCB
	ARB, other combinations
CCB	Dihydropyridine derivatives
	Dihydropyridine derivatives and ACE inhibitors, plain
MRA	Aldosterone antagonists
Thiazide	Thiazides, plain
Venous loop diuretics	Furosemide
	Bumetanide
	Torasemide
β blocking agents selective	β blocking agents selective
Morphine	ATC code: N02AA01
Epinephrine	ATC code: C01CA24
Milrinone	ATC code: C01CE02

Dobutamine	ATC code: C01CA07
Dopamine	ATC code: C01CA04
Norepinephrine	ATC code: C01CA03
Antibacterials	
All	Antibacterials for systemic use Antibacterials for systemic use, anti-inflammatory, and antirheumatic products Antibacterials for systemic use, antigout preparations Antibacterials for systemic use, antibacterials for systemic use
Restricted or special	ATC codes including J01AA02; J01AA05; J01AA08; J01CA09; J01CA10 and J01CG01; J01CA16; J01CF05 and J01CA04; J01CR02; J01CR03; J01CR05; J01DB07; J01DB12; J01DC01; J01DC07; J01DC09; J01DC12; J01DD01; J01DD02; J01DD06; J01DD07; J01DD10; J01DD11; J01DD12; J01DD13; J01DD15; J01DD16; J01DD18; J01DD52; J01DD62; J01DD63; J01DE01; J01DE02; J01DF01; J01DH02; J01DH03; J01DH51; J01DH55; J01DI03; J01FA10; J01FA13; J01GB; J01GB01; J01GB03; J01MA; J01MA01; J01MA02; J01MA06; J01MA07; J01MA08; J01MA09; J01MA10; J01MA14; J01MA16; J01MA18; J01MA22; J01XA; J01XA01; J01XA02; J01XB02; J01XX08
Antimycotics	
All	Antimycotics for systemic use
Restricted or special	ATC codes including J02AA01; J02AC02; J02AC03; J02AX04; J02AX05

ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blockers, CCB – calcium channel blocker, MRA – aldosterone receptor antagonists.

Supplementary Table SII. Details of laboratory tests

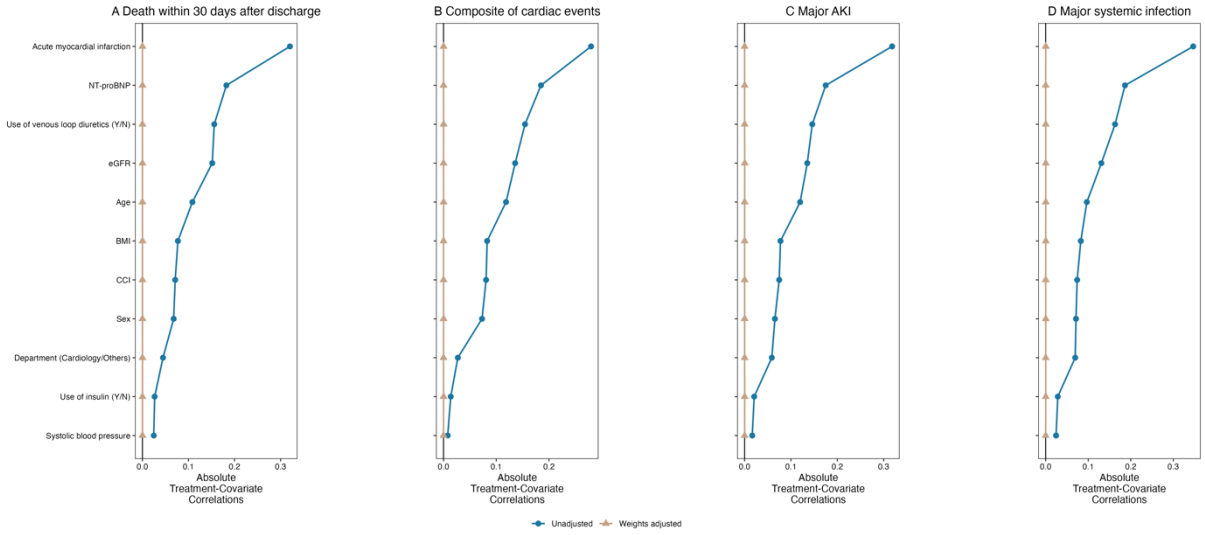
Laboratory tests			
– Low–density lipoprotein – Total cholesterol – High–density lipoprotein – Triglyceride	– Alanine aminotransferase – Aspartate aminotransferase – Hemoglobin – N–terminal pro–B–type natriuretic peptide – Serum creatinine – Leukocytes	– Blood glucose – Glycated hemoglobin A_{1c} – Fasting glucose – 2–hour blood glucose after – 75 g glucose challenge – Random glucose	PH Serum sodium Beta hydroxybutyric acid Urine ketones

Supplementary Table SIII. Identification of comorbidities from admission or discharge diagnosis records using the International Classification of Diseases, 10th Revision (ICD-10) codes, or free text

Comorbidities	ICD-10 codes	Free text
Hypertension	I10 to I15	Free text relating to hypertension; but excluding free text relating to individuals without hypertension, or with or without a family history of hypertension
Ischemic heart disease (IHD)	I20 to I25	Free text describing heart problems caused by narrowed heart arteries, such as myocardial infarction, angina, IHD, or coronary artery stenosis; but excluding free text relating to individuals without IHD, or with or without a family history of IHD
Acute myocardial infarction (AMI)	I21, I22, I23, I24	Free text describing acute myocardial infarction
Stroke	I61, I63, I64	Free text describing brain ischemia or brain hemorrhage; but excluding free text concerning individuals without stroke
Atherosclerotic cardiovascular disease (ASCVD)	I20 to I25, I61, I63, I64	This study only evaluates the most frequently occurring diseases of ASCVD, free text describing IHD, and cerebrovascular disease; but excludes free text describing those without ASCVD
Heart failure	I11.0, I13.0, I13.2, I50	Free text describing heart failure, New York Heart Association (NYHA) class II or III or IV, but excluding free text describing those without heart failure
Viral hepatitis	B15, B16, B17, B18, B19	Free text describing viral hepatitis including acute hepatitis A, acute hepatitis B, other acute viral hepatitis, chronic viral hepatitis and unspecified viral hepatitis
Hemochromatosis	E83.11	Free text describing hemochromatosis
Wilson's disease	E83.01	Free text describing Wilson's disease
Alcoholic liver disease	K70	Free text describing alcoholic liver disease
Toxic liver disease	K71	Free text describing toxic liver disease
Cirrhosis	K74	Free text describing cirrhosis of liver

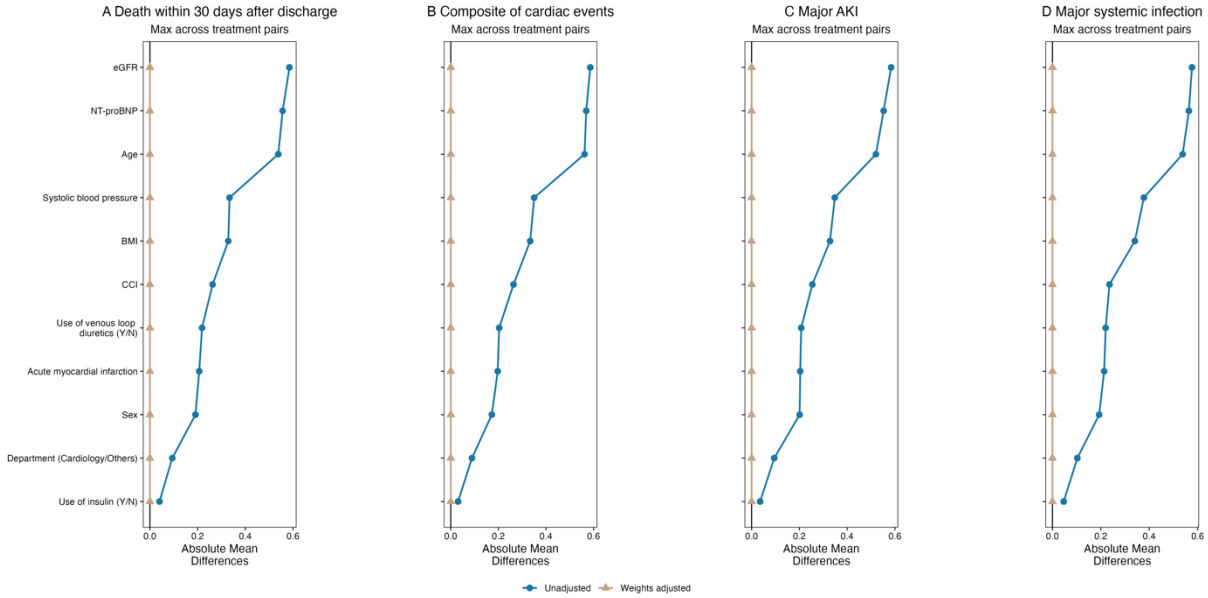
Other or not elsewhere classified liver disease	K72, K73, K75, K76, K77	Free text describing other or not elsewhere classified liver disease

Supplementary Figure S1. Correlations of AST/ALT ratio with covariates before and after applying entropy balancing



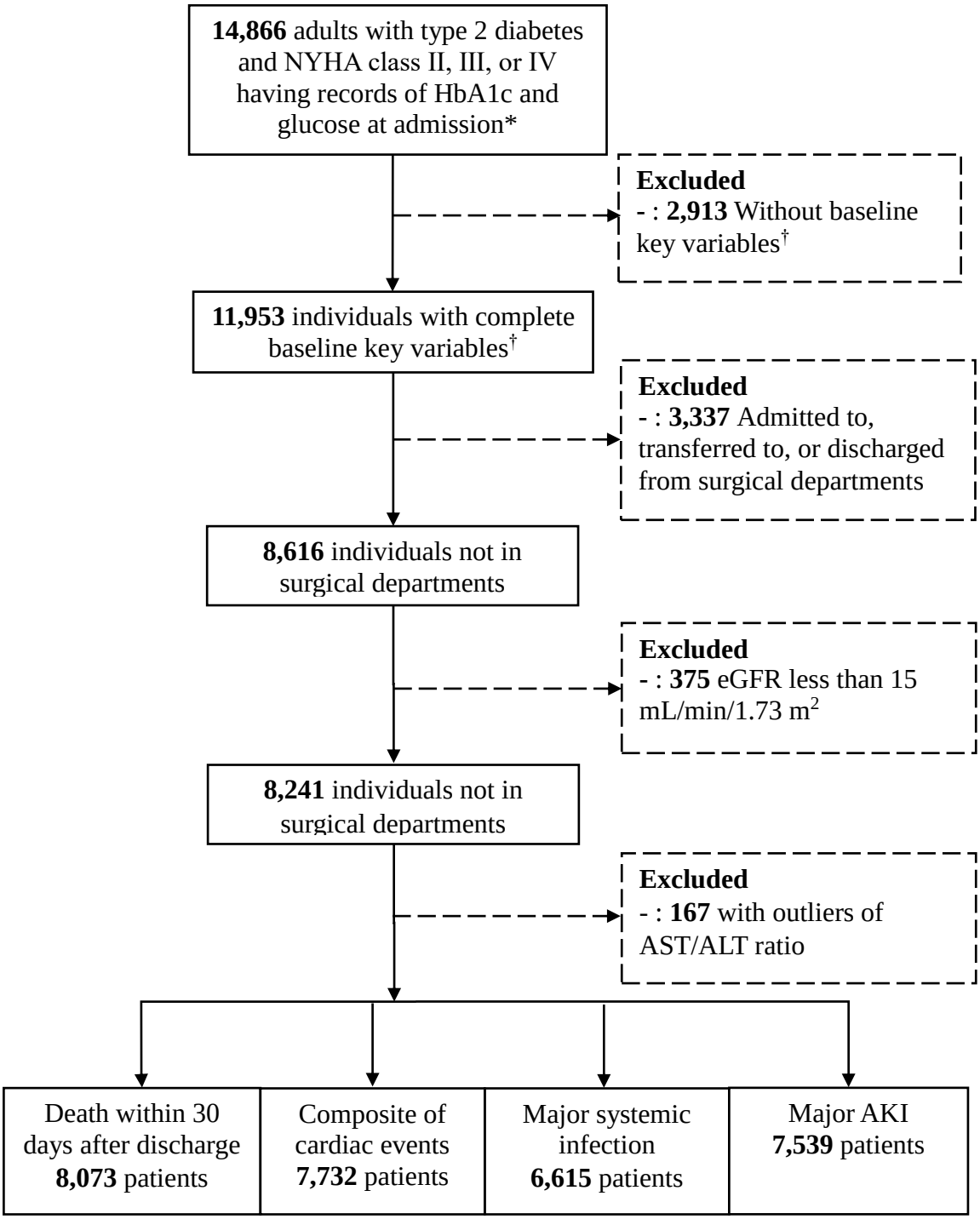
AKI – acute kidney injury, BMI – body mass index, CCI – Charlson Comorbidity Index, Department – admission department (Cardiology vs. others), eGFR – estimated glomerular rate filtration, NT-proBNP – N-terminal pro-B-type natriuretic peptide.

Supplementary Figure S2. Absolute mean difference of covariates across AST/ALT ratio quartiles before and after applying entropy balancing



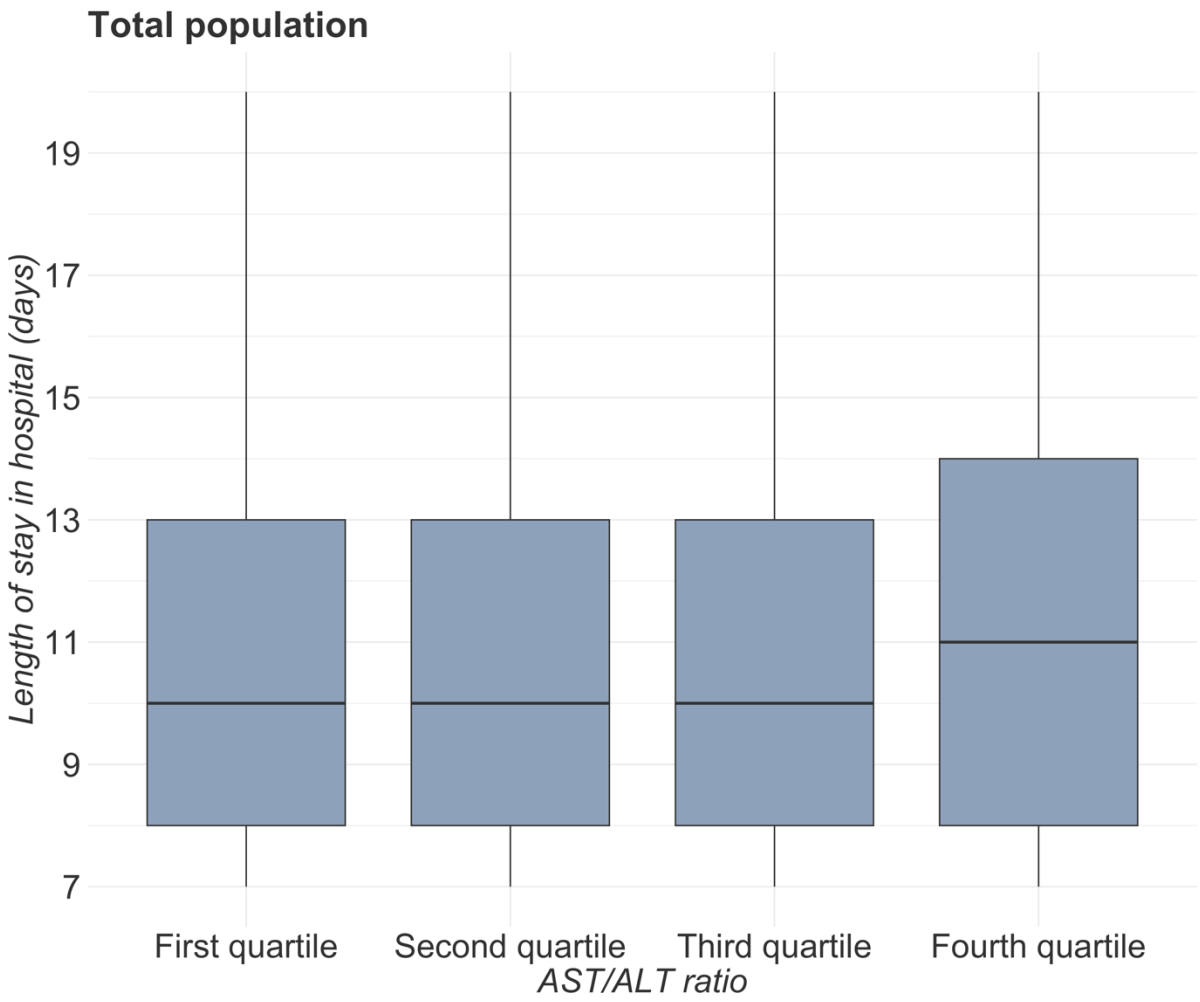
AKI – acute kidney injury, BMI – body mass index, CCI – Charlson Comorbidity Index, Department – admission department (Cardiology vs. others), eGFR – estimated glomerular rate filtration, NT-proBNP – N-terminal pro-B-type natriuretic peptide.

Supplementary Figure S3. Flowchart of selection of the study population



*Adults with type 2 diabetes were diagnosed with NYHA class II, III, or IV at admission or during hospitalization, with available records on diagnosis at discharge, prescription, and blood glucose and glycated hemoglobin A_{1c} at admission, covered by West China Electronic medical record Collaboration Of DiabEtes between 01/01/2011 and 30/06/2019. †Baseline key characteristics include alanine aminotransferase and aspartate aminotransferase. AKI – acute kidney injury, eGFR – estimated glomerular rate filtration, HbA_{1c} – glycated hemoglobin A_{1c}, NYHA – New York Heart Association.

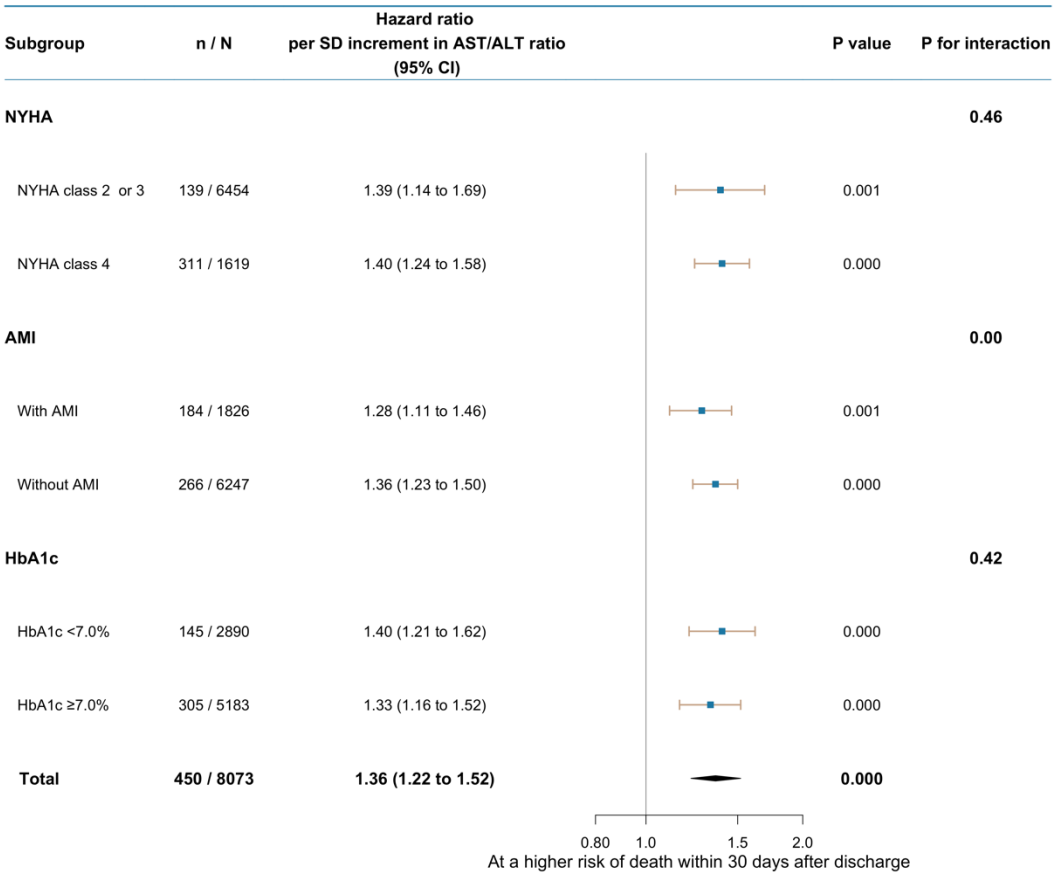
Supplementary Figure S4. Length of stay in hospital across AST/ALT ratio quartiles



ALT – alanine aminotransferase, AST – aspartate aminotransferase.

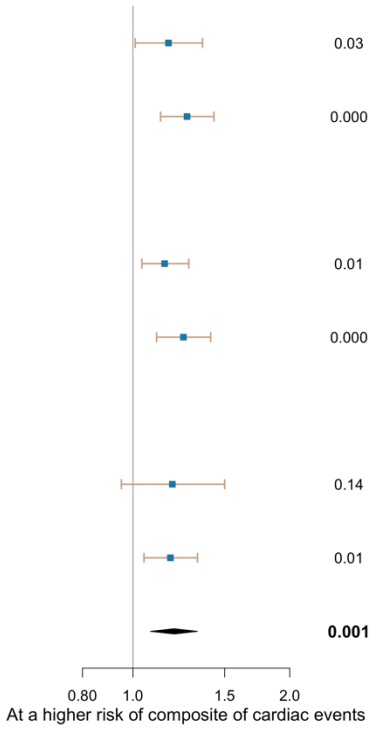
Supplementary Figure S5. Subgroup analyses of the association between AST/ALT ratio and primary outcomes during hospitalization

A. Death within 30 days after discharge



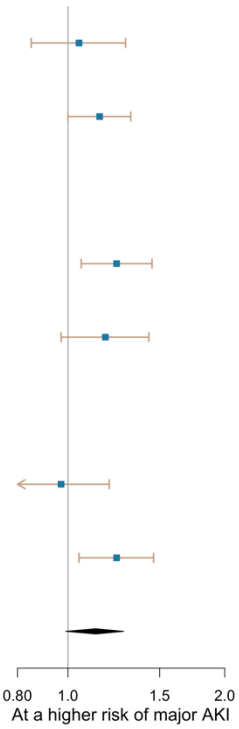
B. Composite of cardiac events

Subgroup	n / N	Hazard ratio per SD increment in AST/ALT ratio (95% CI)	P value	P for interaction
NYHA				**0.58**
NYHA class 2 or 3	425 / 6278	1.17 (1.01 to 1.36)	0.03	
NYHA class 4	421 / 1454	1.27 (1.13 to 1.43)	0.000	
AMI				**0.00**
With AMI	320 / 1600	1.15 (1.04 to 1.28)	0.01	
Without AMI	526 / 6132	1.25 (1.11 to 1.41)	0.000	
HbA1c				**1.00**
HbA1c <7.0%	282 / 2820	1.19 (0.95 to 1.50)	0.14	
HbA1c ≥7.0%	564 / 4912	1.18 (1.05 to 1.33)	0.01	
Total	**846 / 7732**	**1.20 (1.08 to 1.33)**	**0.001**	

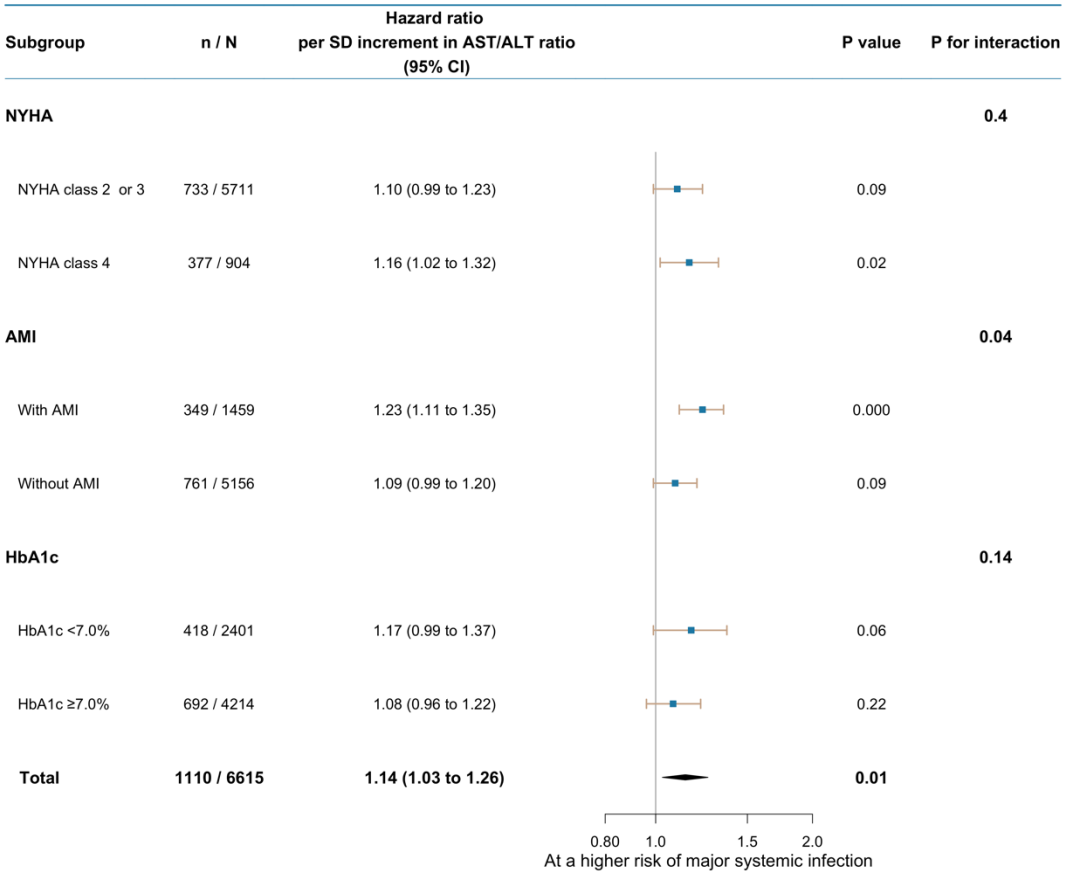


C. Major AKI

Subgroup	n / N	Hazard ratio per SD increment in AST/ALT ratio (95% CI)	P value	P for interaction
NYHA				**0.87**
NYHA class 2 or 3	147 / 6176	1.05 (0.85 to 1.29)	0.68	
NYHA class 4	223 / 1363	1.15 (1.00 to 1.32)	0.05	
AMI				**0.15**
With AMI	134 / 1647	1.24 (1.06 to 1.45)	0.01	
Without AMI	236 / 5892	1.18 (0.97 to 1.43)	0.09	
HbA1c				**0.09**
HbA1c <7.0%	156 / 2727	0.97 (0.79 to 1.20)	0.79	
HbA1c ≥7.0%	214 / 4812	1.24 (1.05 to 1.46)	0.01	
Total	**370 / 7539**	**1.13 (0.99 to 1.28)**	**0.06**	



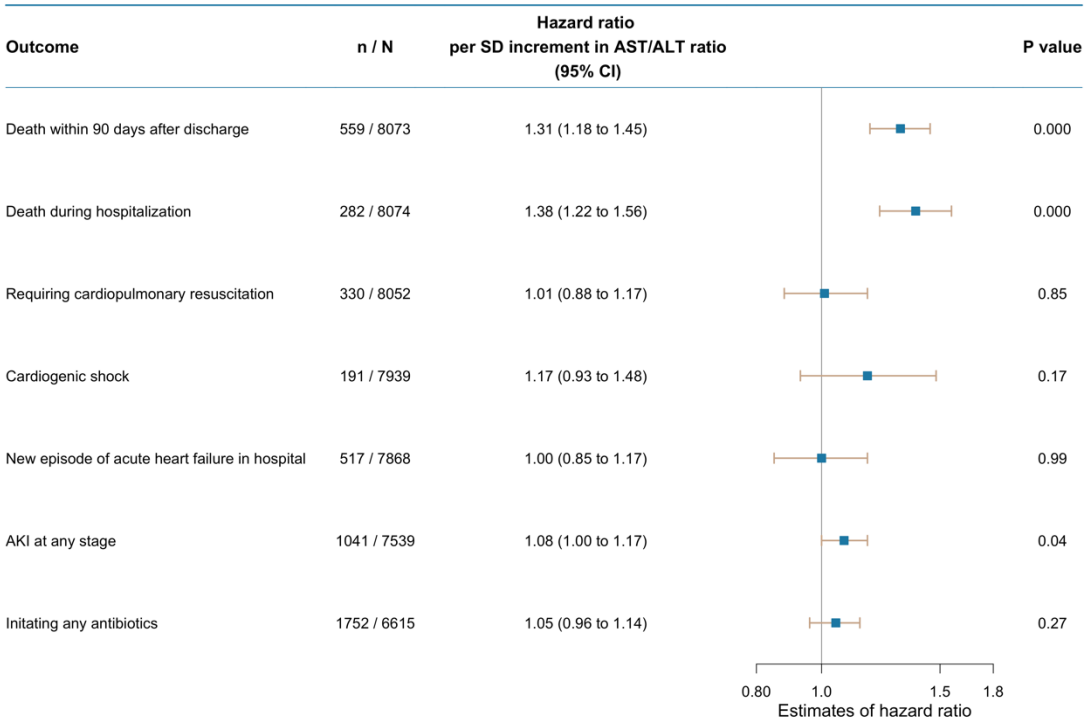
D. Major systemic infection



AKI – acute kidney injury, AMI – acute myocardial infarction, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval, eGFR – estimated glomerular rate filtration, HbA_{1c} – glycated hemoglobin A_{1c}, NYHA – New York Heart Association, SD – standard deviation.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

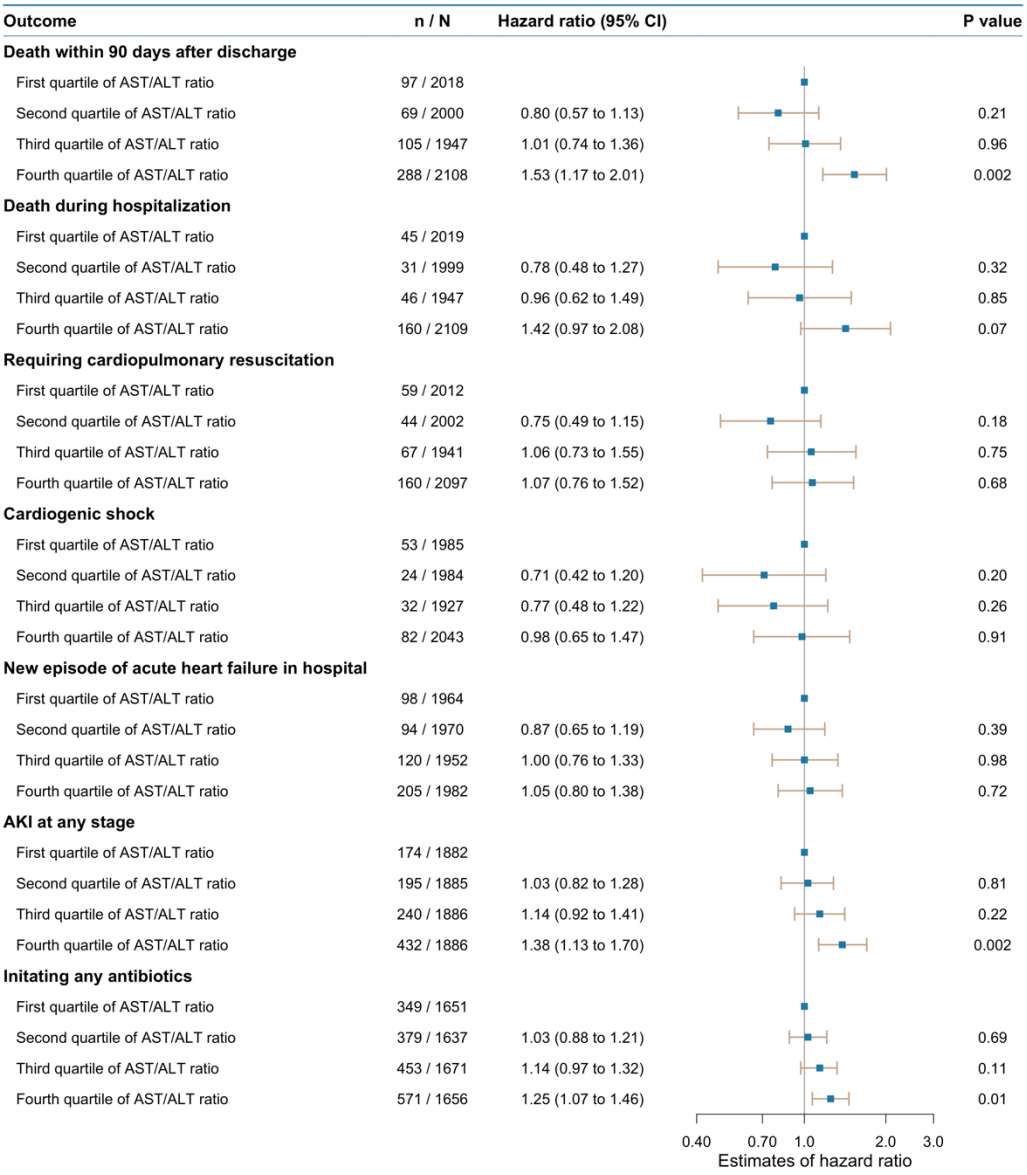
Supplementary Figure S6. Adjusted hazard ratios of AST/ALT ratio with secondary outcomes in the total study population



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval, SD – standard deviation.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

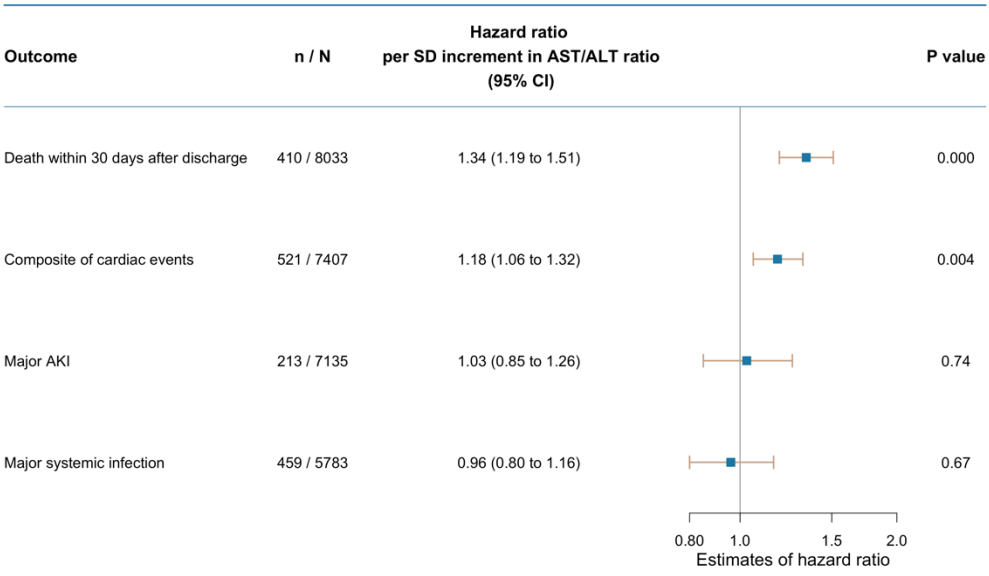
Supplementary Figure S7. Adjusted hazard ratios of AST/ALT ratio quartiles for secondary outcomes in the total study population



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

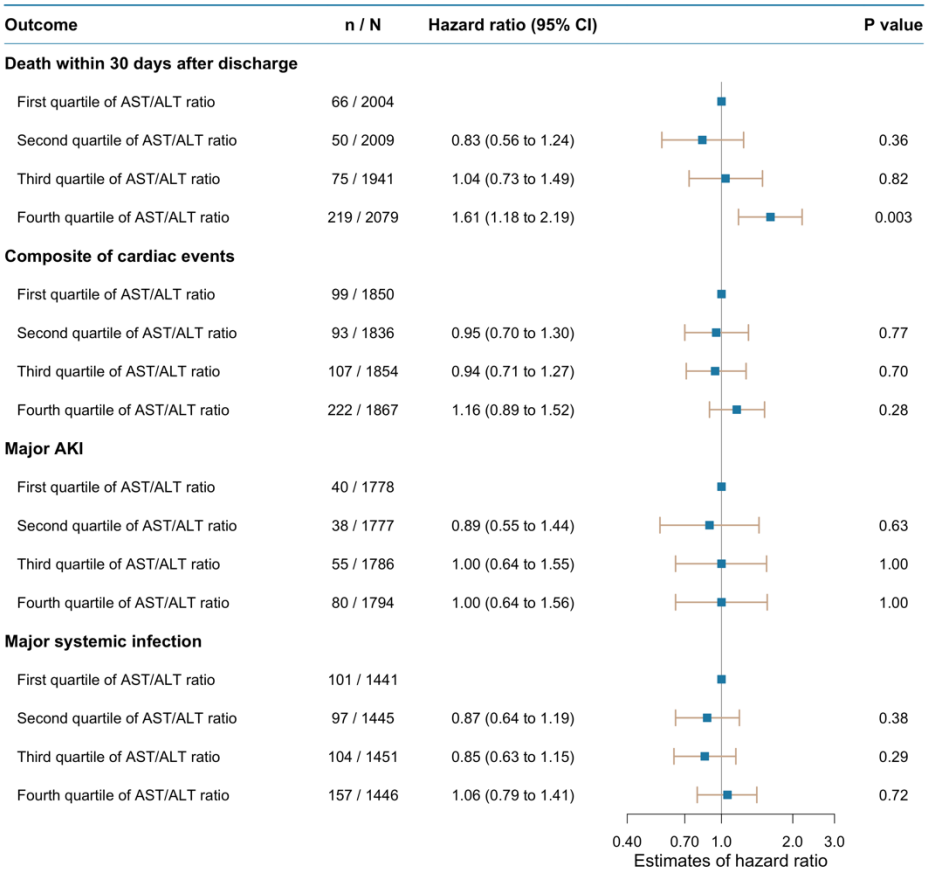
Supplementary Figure S8. Adjusted hazard ratios of AST/ALT ratio with primary outcomes in a sensitivity analysis by excluding adverse events occurred within two calendar days after admission



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval, SD – standard deviation.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

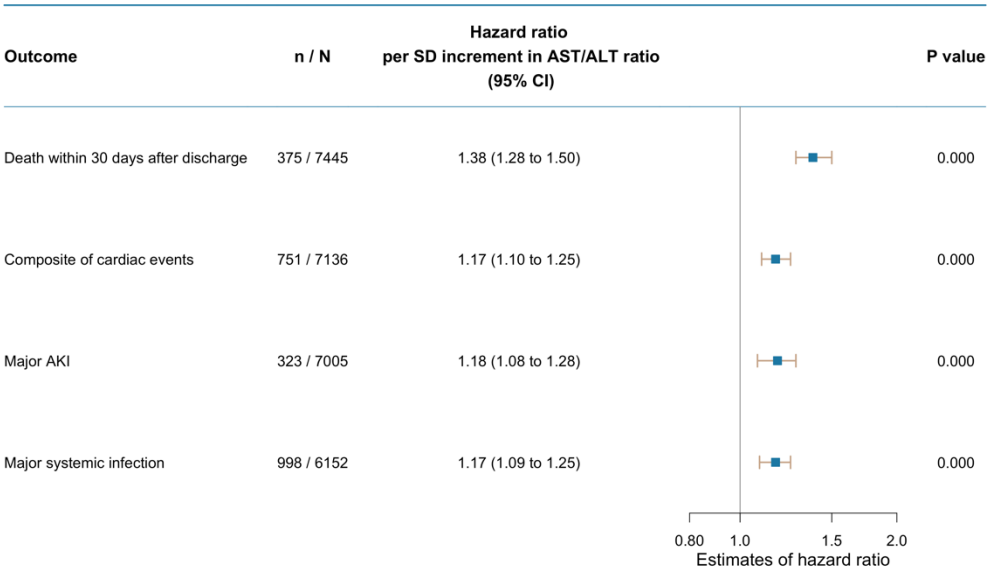
Supplementary Figure S9. Adjusted hazard ratios of AST/ALT ratio quartiles for primary outcomes in a sensitivity analysis by excluding adverse events occurred within two calendar days after admission



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

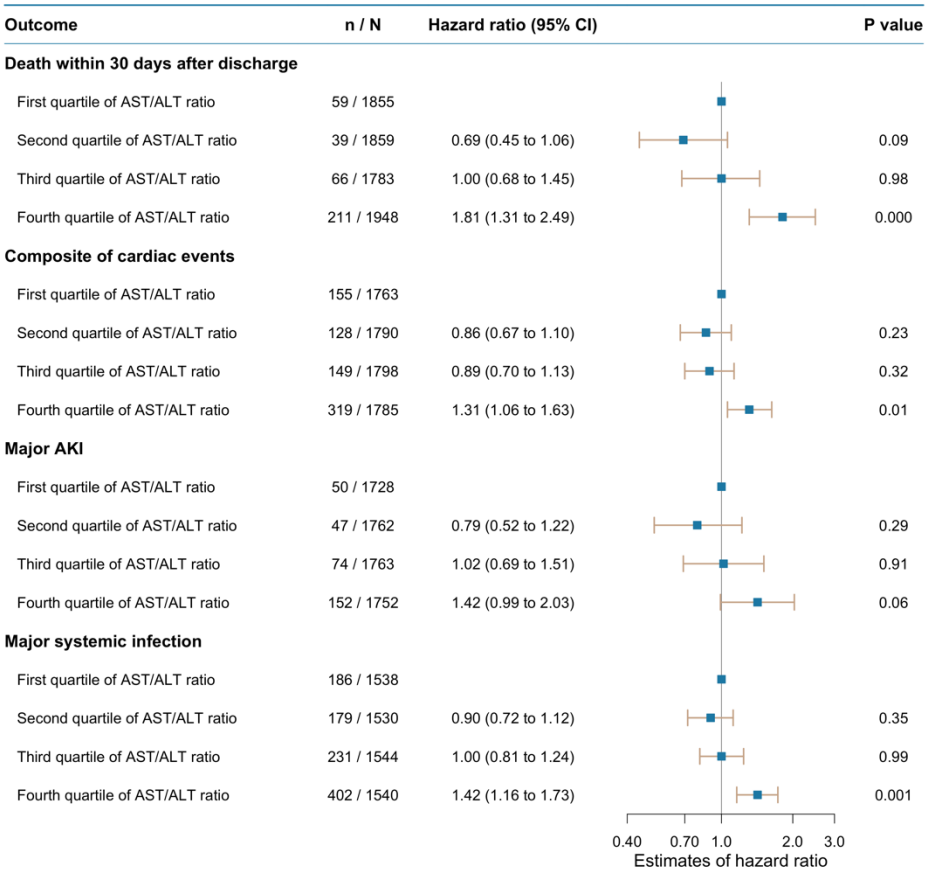
Supplementary Figure S10. Adjusted hazard ratios of AST/ALT ratio with primary outcomes in a sensitivity analysis by excluding patients with common liver diseases



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval, SD – standard deviation.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level of 7.0% at admission is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.

Supplementary Figure S11. Adjusted hazard ratios of AST/ALT ratio quartiles for primary outcomes in a sensitivity analysis by excluding patients with common liver diseases



AKI – acute kidney injury, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval.

All analyses were adjusted for age, sex, body mass index, baseline systolic blood pressure, baseline estimated glomerular filtration rate, baseline N-terminal pro-B-type natriuretic peptide, admission department (Department of Cardiology/other), Charlson Comorbidity Index, with or without acute myocardial infarction at baseline, whether insulin was used at baseline (yes vs. no), and whether venous loop diuretics were used at baseline (yes vs. no). HbA_{1c} level at admission of 7.0% is equal to 53.0 mmol/mol. Patients with impaired kidney function at baseline were identified by eGFR at baseline < 60 ml/min/1.73 m^2.