

Supplementary Material

Title: CRISP: A Causal Relationships-Guided Deep Learning Framework for Advanced ICU Mortality Prediction

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1. Supplementary Tables

STable 1. The patient characteristics of the WCHSU cohort. For continuous variables, data is presented in means and standard deviation. Mann–Whitney U test was used to compare the differences. For categorical variables, data is presented in frequencies and percentages. Chi square test was used to test for association. BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CHD, Coronary Heart Disease; IHD, Ischemic Heart Disease; CHF, Congestive Heart Failure;CKD, Chronic Kidney Disease; ASA-PS, American Society of Anesthesiologists; AST, glutamic oxalacetic transaminase; ALT, Alanine transaminase;WBC, White Blood Cell Count; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; LOS, length of stay in the ICU.

Patients characteristics on WCHSU dataset.				
Variable	Total	Majority set &Minority set		
	n=10984	Survival(n=10885)	Mortality(n=99)	P-value
Mortality,n(ratio)	99(0.009)	0	99	
Patient demographics				
Age(Mean±SD)	71.98±5.74	71.96±5.72	73.78±7.35	0.05
Gender,n(ratio)				0.007
	Male	6189(0.56)	6120(0.56)	69(0.7)
	Female	4795(0.44)	4765(0.44)	30(0.3)
Height(cm)(Mean±SD)	160.23±8.10	160.22±8.11	161.93±7.63	0.04
Weight(kg)(Mean±SD)	60.32±10.34	60.34±10.33	57.63±10.88	0.003
BMI(kg/m2)(Mean±SD)	23.45±3.48	23.47±3.47	21.92±3.51	0.000002
LOS(h)(Mean±SD)	3.28±1.85	3.27±1.84	4.94±2.86	3E-10
Comorbidities,n(ratio)				
Anemia	2990(0.27)	2921(0.27)	30(0.3)	1.45E-21
Hypertension	4055(0.37)	4019(0.37)	36(0.37)	0.21
Arrhythmia	859(0.08)	843(0.08)	16(0.16)	0.0001
COPD	490(0.04)	482(0.04)	8(0.08)	4E-10
CHD	44(0.004)	43(0.004)	1(0.01)	0.57
Diabetes	1074(0.1)	1062(0.1)	12(0.12)	0.89
Liver disease	350(0.03)	348(0.03)	2(0.02)	0.51
IHD	397(0.04)	390(0.4)	7(0.07)	0.004
CHF	40(0.004)	37(0.003)	3(0.03)	0.000009
CKD	134(0.01)	131(0.01)	3(0.03)	0.1
Laboratory tests and Vital signs(Mean±SD)				
Albumin(g/L)	41.48±4.55	41.49±4.51	36.45±5.64	2E-20
AST(IU/L)	22.73±8.81	22.67±8.75	28.51±12.34	0.00002
ALT(IU/L)	20.32±12.33	20.28±12.28	24.72±16.35	0.09
Total Bilirubin(μmol/L)	12.29±5.18	12.27±5.16	14.60±6.61	0.0009
Potassium(mmol/L)	4.01±0.37	4.01±0.37	4.00±0.45	0.75
Creatinine(μmol/L)	77.16±19.41	77.09±19.33	84.42±26.08	0.005
Glucose(mmol/L)	5.60±1.25	5.59±1.24	6.35±1.85	0.00009
WBC (×10 ⁹ /L)	5.96±1.73	5.95±1.72	6.95±2.42	0.00002
Hemoglobin(g/L)	127.95±19.01	128.09±18.90	112.50±24.11	3E-11
Platelet(×10 ⁹ /L)	178.38±61.50	178.45±61.38	170.30±73.61	0.22
PT(s)	10.94±0.85	10.94±0.85	11.66±0.94	4E-14
PTT(s)	27.61±27.60	27.60±2.46	28.41±3.09	0.007
INR	1.00±0.41	1.00±0.41	1.16±0.38	9E-16
Heart rate(bpm)	78.96±12.52	78.91±12.49	83.48±14.93	0.0005
Respiratory rate(bpm)	19.42±1.24	19.42±1.24	19.47±1.50	0.06
Systolic BP(mmHg)	133.99±17.36	134.06±17.30	126.24±21.53	0.0002
Diastolic BP(mmHg)	79.35±11.17	79.42±11.13	72.68±13.42	0.0000001
SPO2(%)	97.42±3.23	97.43±3.21	95.70±4.77	0.0002
Body temperature(°C)	36.40±0.92	36.40±0.92	36.46±0.30	0.05

STable 2. Medical Coding Reference Table: Diagnosis, Procedure and Medicine Codes and Their Clinical Interpretations.

Type	ID	Meaning
Diagnose	Z85	Personal history of malignant neoplasm
	J98	Other respiratory disorders
	I25	Chronic ischemic heart disease
	F10	Alcohol related disorders
	J69	Pneumonitis due to solids and liquids

	J45	Asthma
	J18	Pneumonia, unspecified organism
	E89	Postprocedural endocrine and metabolic complications and disorders, not elsewhere classified
	D69	Purpura and other hemorrhagic conditions
	I95	Hypotension
	I10	Essential (primary) hypertension
	E66	Overweight and obesity
	E87	Other disorders of fluid, electrolyte and acid-base balance
	R78	Findings of drugs and other substances, not normally found in blood
	A40	Streptococcal sepsis
	N17	Acute kidney failure
	F41	Other anxiety disorders
	N18	Chronic kidney disease (CKD)
	G47	Sleep disorders
	E11	Type 2 diabetes mellitus
	R09	Other symptoms and signs involving the circulatory and respiratory system
	I47	Paroxysmal tachycardia
	K70	Alcoholic liver disease
	9971	Cardiac complications, not elsewhere classified
	Z95	Presence of cardiac and vascular implants and grafts
	I21	Acute myocardial infarction
	I12	Hypertensive chronic kidney disease
	F32	Depressive episode
	I34	Nonrheumatic mitral valve disorders
	T78	Adverse effects, not elsewhere classified
	K22	Other diseases of esophagus
	I50	Heart failure
	J44	Other chronic obstructive pulmonary disease
	D64	Other anemias
	R00	Abnormalities of heart beat
	E78	Disorders of lipoprotein metabolism and other lipidemias
	N39	Other disorders of urinary system
	K92	Other diseases of digestive system
Procedure	9604	Insertion of endotracheal tube
	3722	Left heart cardiac catheterization
	3723	Combined right and left heart cardiac catheterization
	225966	Nasal Swab, procedureevents, 6-Cultures
	8856	Coronary arteriography using two catheters

	224270	Dialysis Catheter, procedureevents, Access Lines - Invasive
	3995	Hemodialysis
	224385	Intubation, procedureevents, 1-Intubation/Extubation
	3615	Single internal mammary-coronary artery bypass
	225402	EKG, procedureevents, 4-Procedures
	4513	Other endoscopy of small intestine
	8872	Diagnostic ultrasound of heart
	9390	Non-invasive mechanical ventilation
	9904	Transfusion of packed cells
	3891	Arterial catheterization
	3893	Venous catheterization, not elsewhere classified
	225401	Blood Cultured, procedureevents, 6-Cultures
	3897	Central venous catheter placement with guidance
	9915	Parenteral infusion of concentrated nutritional substances
	224264	PICC Line, procedureevents, Access Lines - Invasive
	966	Enteral infusion of concentrated nutritional substances
	9671	Continuous invasive mechanical ventilation for less than 96 consecutive hours
	9672	Continuous invasive mechanical ventilation for 96 consecutive hours or more
	221217	Ultrasound, procedureevents, 5-Imaging
	3961	Extracorporeal circulation auxiliary to open heart surgery
	221214	CT scan, procedureevents, 5-Imaging
	225792	Invasive Ventilation, procedureevents, 2-Ventilation
	225454	Urine Culture, procedureevents, 6-Cultures
	225752	Arterial Line, procedureevents, Access Lines - Invasive
	227194	Extubation, procedureevents, 1-Intubation/Extubation
	3324	Closed [endoscopic] biopsy of bronchus
Medicine	A02AC	Calcium compounds
	A02BA	H2-receptor antagonists
	A02BC	Proton pump inhibitors
	A04AA	Serotonin (5HT3) antagonists
	A06AB	Contact laxatives
	A06AD	Osmotically acting laxatives
	A07AA	Antibiotics
	B01AA	Vitamin K antagonists
	B01AC	Platelet aggregation inhibitors excl. heparin
	C01BD	Antiarrhythmics, class III
	C03CA	Sulfonamides, plain
	C07AB	Beta blocking agents, selective

	C09AA	ACE inhibitors, plain
	J01MA	Fluoroquinolones
	N02BE	Anilides
	N05BA	Benzodiazepine derivatives

STable 3. The range for handling outliers in the observed features during the ICU stay.

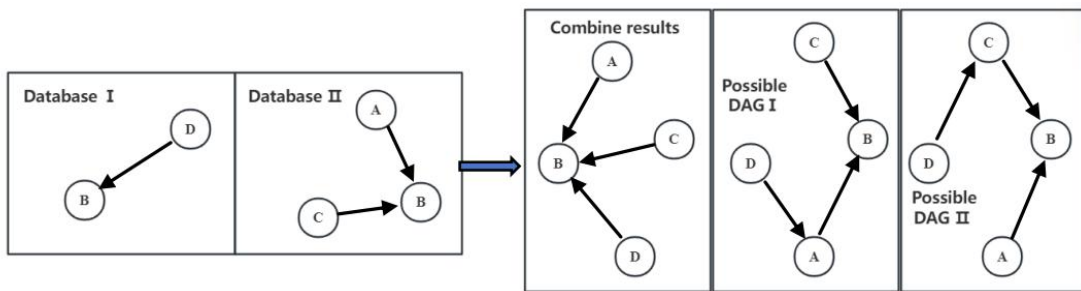
Features	Outlier Low	Outlier High	Unit
Alanine Aminotransferase	2	10000	IU/L
Alkaline Phosphate	20	3625	IU/L
Albumin	0.6	6	None
Anion gap	5	50	None
Aspartate Aminotransferase	6	20000	IU/L
Bicarbonate	0	60	mEq/L
Bilirubin	0.1	60	None
Blood urea nitrogen	0	250	mg/dL
Calcium	0	40	mg/dL
Cholesterol	32	600	mg/dL
Creatinine	0.1	60	None
Diastolic blood pressure	0	375	mmHg
Glasgow coma scale total	3	15	score
Glucose	33	2000	None
Heart Rate	0	390	bpm
Hemoglobin	0	25	g/dL
MCHC	0	36	mg/dL
Mean blood pressure	14	330	mmHg
Oxygen saturation(SpO ₂)	0	100	%
Partial thromboplastin time	18.8	150	seconds
pH	6.3	8.4	None
Platelets	0	2000	mL
Positive end-expiratory pressure set	0	25	cmH ₂ O
Prothrombin time	9.9	97.1	None
Red Cell Distribution Width	0	22	%
Respiratory rate	0	300	insp/min
SaO ₂	90	100	%
Sodium	50	225	None
Systolic blood pressure	0	375	mmHg
Temperature	26	45	°C
White blood cell count	0	1000	cells/ μ L

STable 4. The top 15 features for the CRISP model on the MIMIC-III test set. The 'Pro_' prefix denotes procedures, 'Diag' refers to diagnoses, and 'Drug' represents the medications used. The corresponding details for each code can be found in STable S2.

Rank	Feature
1	Pro_9604
2	BUN_min
3	GCS_max
4	Diag_J98
5	SpO2
6	AG_min
7	Creatinine_min
8	SBP_min
9	AGE
10	Pro_9671
11	Pro_9672
12	HCO3_min
13	Drug_C07AB
14	Diag_A40
15	RR_min

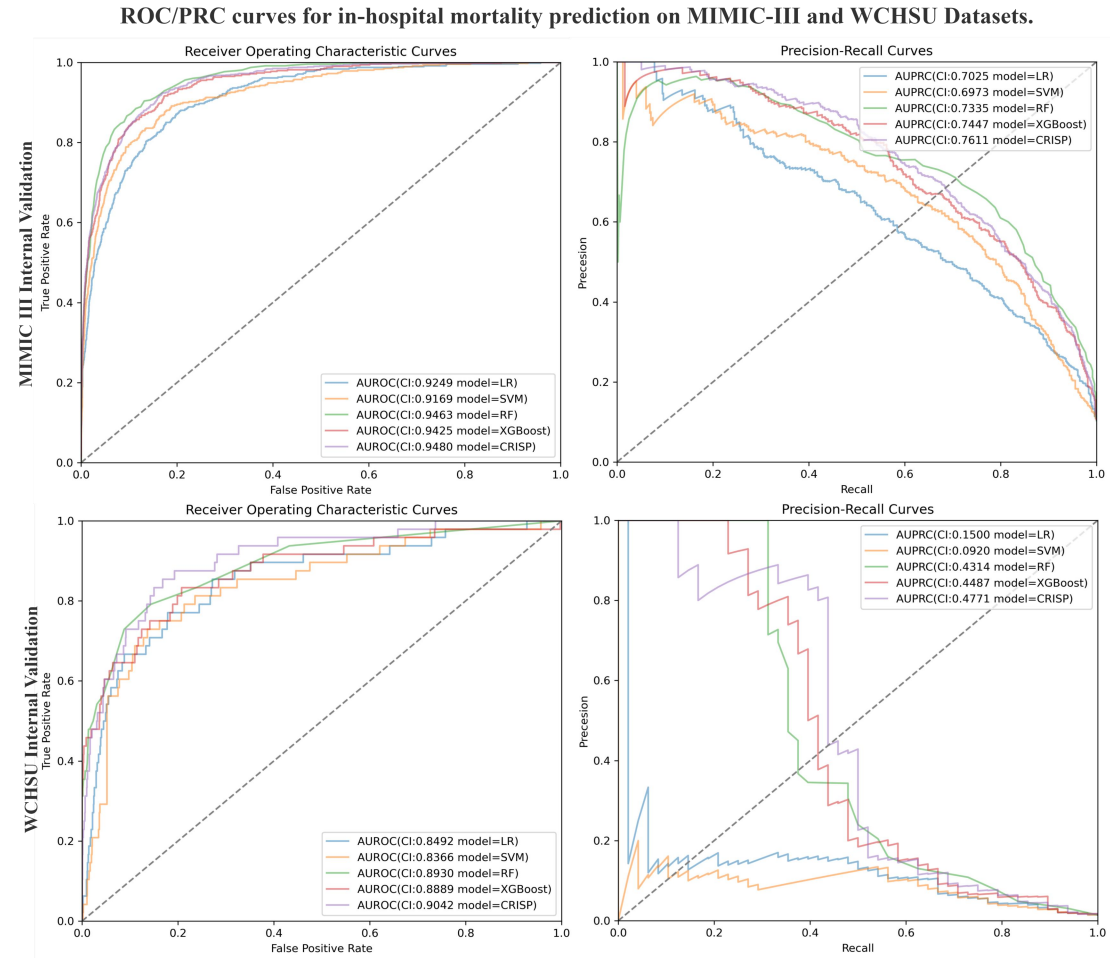
2. Supplementary Figures

SFigure 1. Simulating the merging of causal graphs between datasets. A, B, C, and D represent the features.



In SFigure 2, aside from (1) the accuracy of causal relationships within each dataset and (2) the validity of the methods used for causal graph merging (e.g., how to resolve edge conflicts), we believe there is another critical limitation: when a feature, D, exists only in dataset I, its true causal relationships with A, B, and C cannot be determined in dataset II because D is not present there. Simply merging causal graphs may result in the omission or misinterpretation of true causal relationships. Therefore, in this study, we chose not to adopt a method that separately learns causal relationships within each of the three datasets and merges them.

SFigure 2. The performance of the separately trained CRISP model is evaluated on MIMIC-III_test and WCHSU_test. ROC and PRC curves are presented for in-hospital mortality prediction on both datasets.



4. Supplementary Definitions

SDefinition 1 (*Causal Directed Acyclic Graph; Causal DAG*[1,2,3]). A causal directed acyclic graph (DAG) is a directed graph that represents causal relationships between variables. In this graph, nodes represent variables, and directed edges (arrows) indicate causal influences from one variable to another. The acyclic nature of the graph means that there are no cycles; that is, no variable can causally influence itself, either directly or indirectly. This structure is fundamental in causal inference, as it allows for the visualization and analysis of complex causal relationships within a system.

SDefinition 2 (*Front-Door Criterion*[1,2,3]). The front-door criterion is a method used in causal inference to identify causal effects when certain conditions are met. It involves finding a set of variables that satisfy the following conditions:

- Intermediary Role:** The set of variables mediates the effect of the treatment on the outcome.
- No Back-Door Paths:** There are no unblocked back-door paths from the treatment to the outcome through the mediator.

- c. No Confounding of the Mediator: The mediator is not confounded with the treatment or the outcome.

When these conditions are satisfied, the front-door criterion allows for the estimation of the causal effect of the treatment on the outcome by adjusting for the mediator.

Definition 3 (*Propensity Score Matching*[4,5,6]). Propensity score matching is a statistical technique used in observational studies to estimate the effect of a treatment or intervention. It involves pairing each treated unit with one or more non-treated units that have similar propensity scores—defined as the probability of receiving the treatment given a set of observed covariates. By matching treated and non-treated units with similar propensity scores, the method aims to reduce confounding and mimic the conditions of a randomized controlled trial, thereby providing a more accurate estimate of the treatment effect.

Definition 4 (*Average Treatment Effect*, ATE [7,8,9]). The average treatment effect (ATE) refers to the average difference in outcomes between units assigned to the treatment and those assigned to the control group. It is a fundamental concept in causal inference, used to estimate the effect of a treatment or intervention on a population. The ATE is calculated as the difference between the expected outcome under treatment and the expected outcome under control, averaged over the entire population.

References:

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