Optimal Hemoglobin Thresholds for ICU Transfusion: A Target Trial Emulation in a Large Electronic Medical Record-Based Real-World Database

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COI Disclosure Information

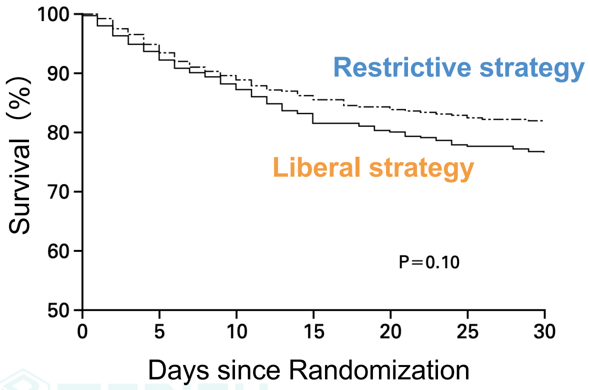
Presenter: Takahiro Kinoshita

The presenter is the founder of MeDiCU, Inc., which develops and manages the database used in this study. The other authors declare no conflicts of interest. No financial support was received for this study.

Restrictive Transfusion (Hb: 7–8 g/dL) or Liberal Transfusion (Hb: 9–10 g/dL)?

Favors restrictive

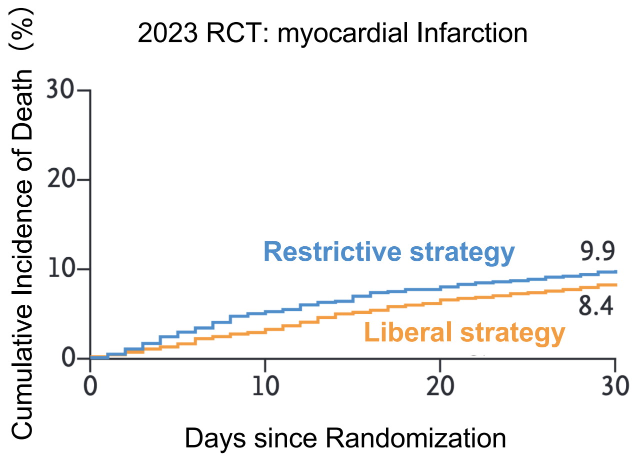
1999 RCT: all ICU admissions



N Engl J Med. 1999;340:409-17.

Favors liberal

2023 RCT: myocardial Infarction



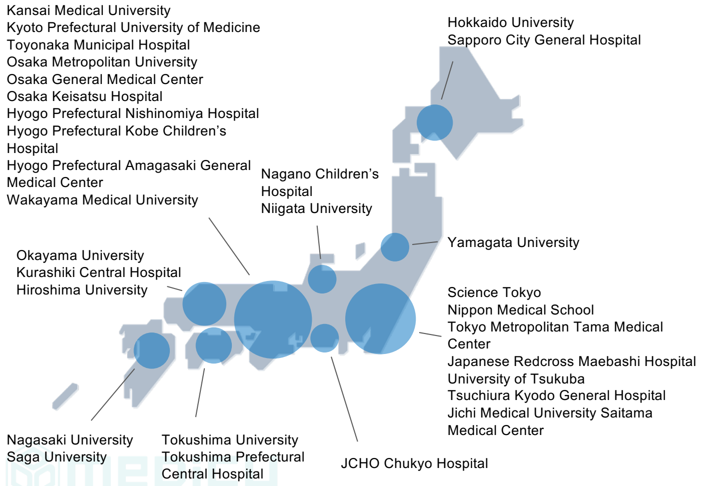
N Engl J Med. 2023;389:2446-2456.

Objective

To investigate the optimal hemoglobin (Hb) threshold for initiating red blood cell transfusion in ICU patients

Methods: Data Source

IRB approved (34 institutions)



The Japanese multi-center critical care database **"OneICU."**

- Study period: Feb 2013 – May 2025
- **Time-series data available** for vital signs, lab results, and interventions
- Second largest cases; largest vital sign measurements worldwide

1) Kinoshita T, et al. Crit Care Med. 2025 in revision

Target Trial Specification/Emulation

Inclusion:
Hb first falls < 9 g/dL

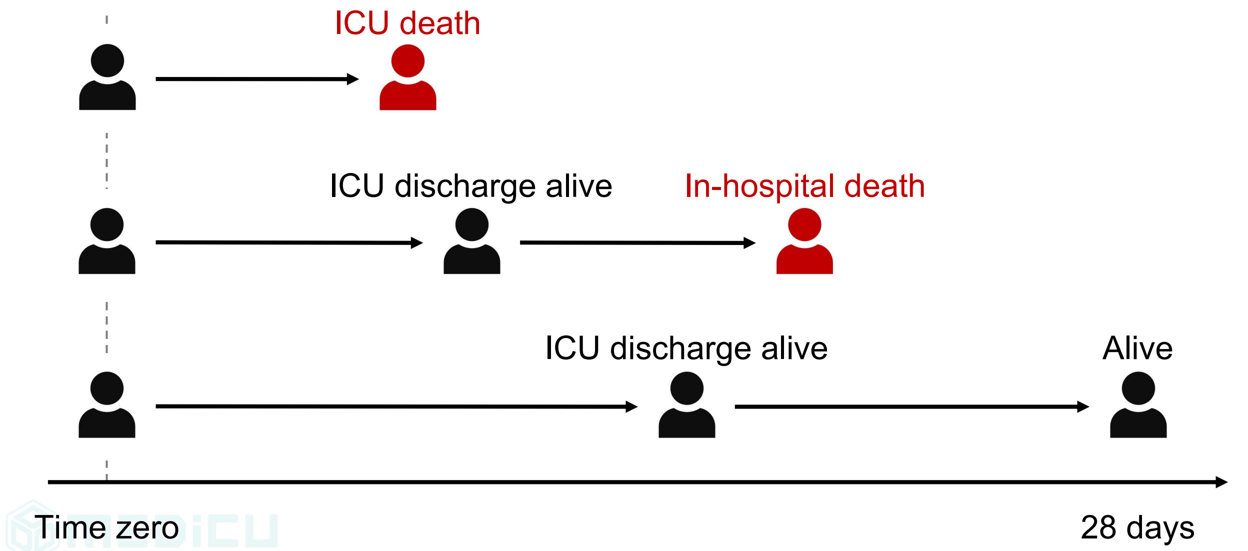
Transfuse if **Hb < 9 g/dL**
otherwise withhold

Transfuse if **Hb < 8 g/dL**
otherwise withhold

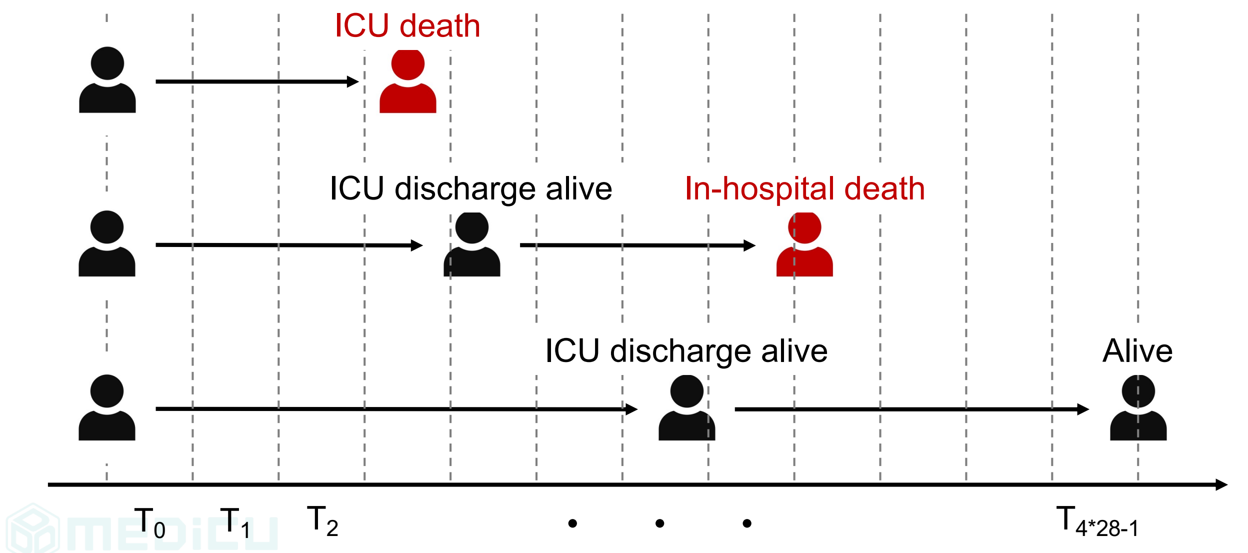
Transfuse if **Hb < 7 g/dL**
otherwise withhold

Emulated a hypothetical RCT to assign patients to one of three transfusion strategies

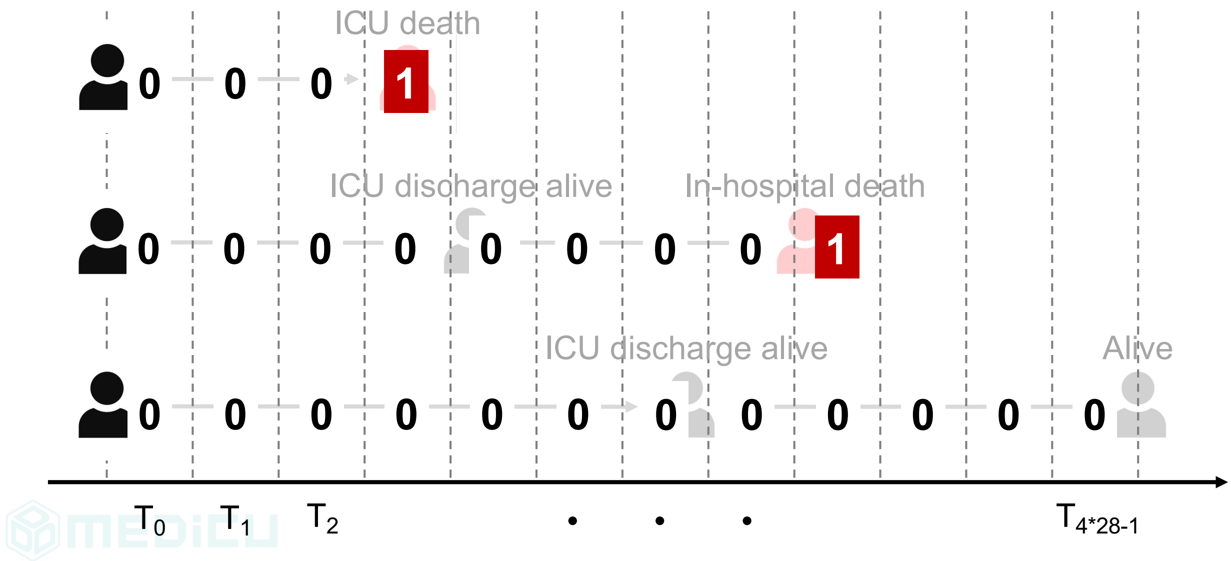
Follow-up until ICU Death, In-hospital Death, or Day 28



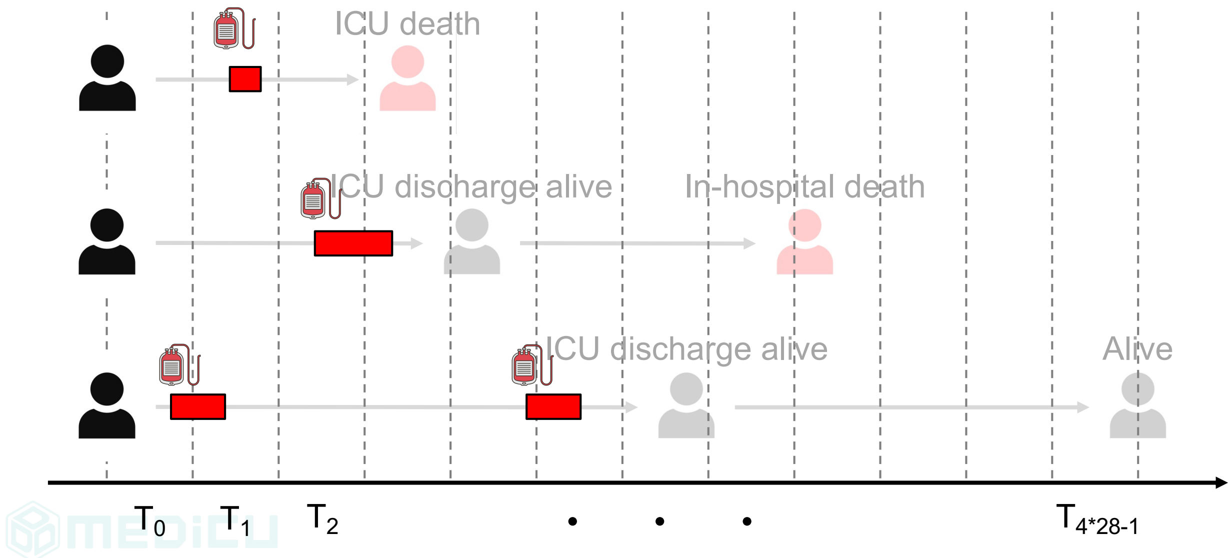
Split Observation Period into **6-Hour** Time Windows



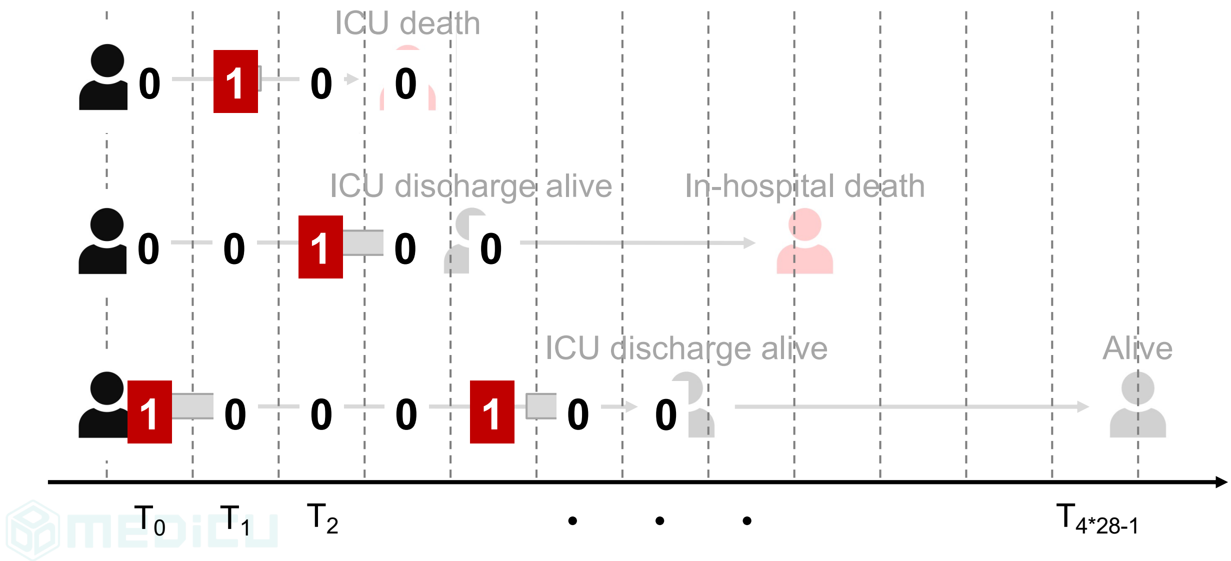
Obtained Binary **Outcomes** (ICU or In-hospital Death)



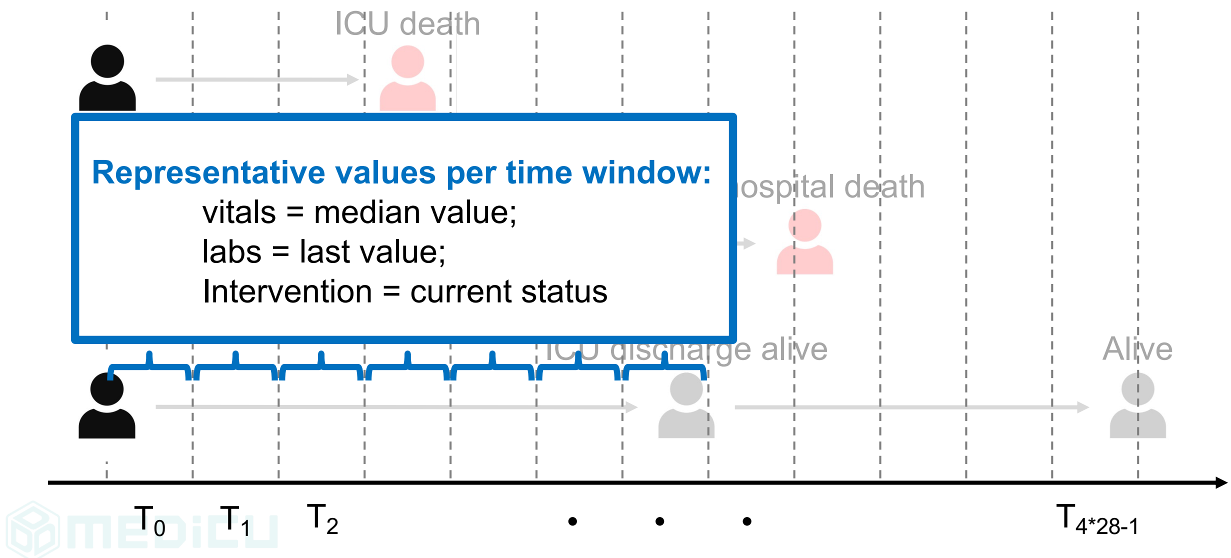
Obtained Binary **Treatment** (Transfusion Initiated)



Obtained Binary **Treatment** (Transfusion Initiated)



Obtained **Covariates** (Vitals, Labs, Ventilator, Catecholamine)



Three Models to Estimate Outcomes Inside and Outside the ICU

ICU mortality model

ICU live discharge model

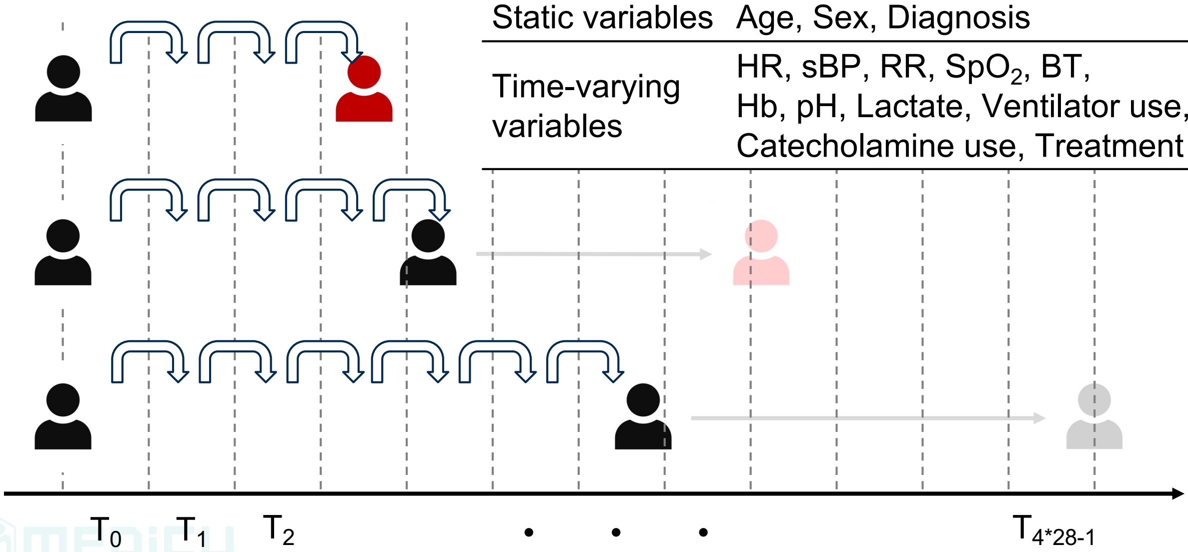
Static variables	Age, Sex, Diagnosis
Time-varying variables	HR, sBP, RR, SpO_2, BT, Hb, pH, Lactate, Ventilator use, Catecholamine use, Treatment

Post-ICU mortality model

Static variables	Age, Sex, Diagnosis
Time-fixed variables at ICU discharge	HR, sBP, RR, SpO2, BT, Hb, pH, Lactate, Ventilator use, Catecholamine use, Cumulative transfusion amount

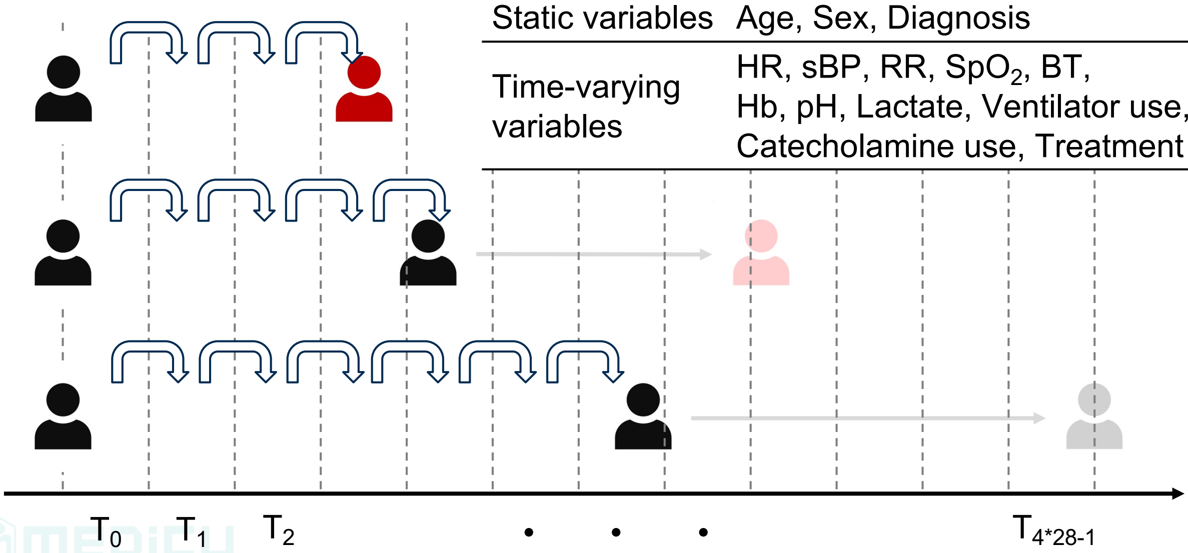
Treatment + Static Variables + Time-varying Variables to Estimate **the Hazard of Death in the Next Time Window**

Static variables	Age, Sex, Diagnosis
Time-varying variables	HR, sBP, RR, SpO_2, BT, Hb, pH, Lactate, Ventilator use, Catecholamine use, Treatment



Treatment + Static variables + Time-varying Variables to Estimate **the Hazard of Live Discharge in the Next Time Window**

Static variables	Age, Sex, Diagnosis
Time-varying variables	HR, sBP, RR, SpO_2, BT, Hb, pH, Lactate, Ventilator use, Catecholamine use, Treatment



Three Models to Estimate Outcomes Inside and Outside the ICU

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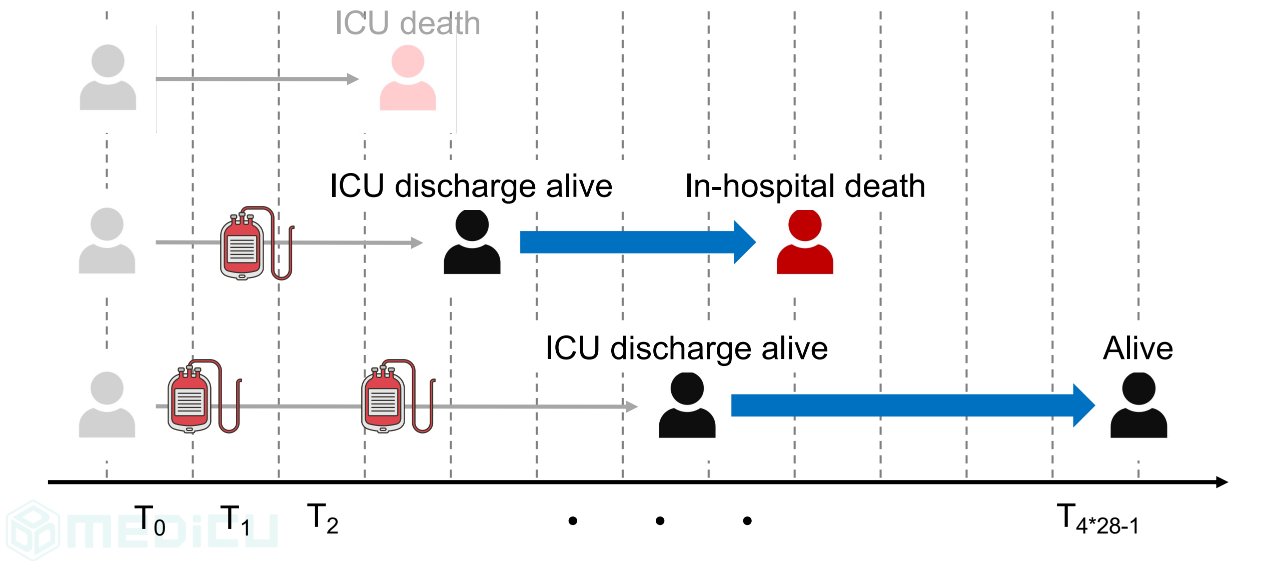
Post-ICU mortality model

Static variables	Age, Sex, Diagnosis
Time-fixed variables at ICU discharge	HR, sBP, RR, SpO2, BT, Hb, pH, Lactate, Ventilator use, Catecholamine use, Cumulative transfusion amount

Cumulative Treatment + Static Variables + Time-fixed Variables to Estimate **the Hazard of Death after ICU Discharge**



Estimated Hazards for ICU Death and Live ICU Discharge under each Strategy using **g-formula**

9g/dL	Tx.	1	0	0	1	0	0	1	0	0	0	0	0
	Hb	8.2	9.6	9.4	9.2	9.1	9.3	8.8	9.9	9.7	9.5	9.3	9.4
	Death		0.05	0.03	0.05	0.03	0.05	0.03	0.05	0.03	0.05	0.03	0.03
	Disch.		0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.02
8g/dL	Tx.	0	1	0	0	0	0	0	0	1	0	0	0
	Hb	8.2	7.8	9.2	9.1	8.8	8.4	8.6	8.1	7.6	9.2	8.8	8.9
	Death		0.06	0.02	0.04	0.06	0.04	0.06	0.05	0.05	0.06	0.04	0.03
	Disch.		0.03	0.01	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.02
7g/dL	Tx.	0	0	0	0	0	0	1	0	0	0	0	0
	Hb	8.2	7.7	7.3	7.5	7.1	7.4	6.9	8.0	7.7	7.6	7.4	7.7
	Death		0.07	0.08	0.06	0.07	0.06	0.07	0.06	0.06	0.05	0.08	0.06
	Disch.		0.02	0.01	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.02

T_0 T_1 T_2 • • • T_{4*28-1}

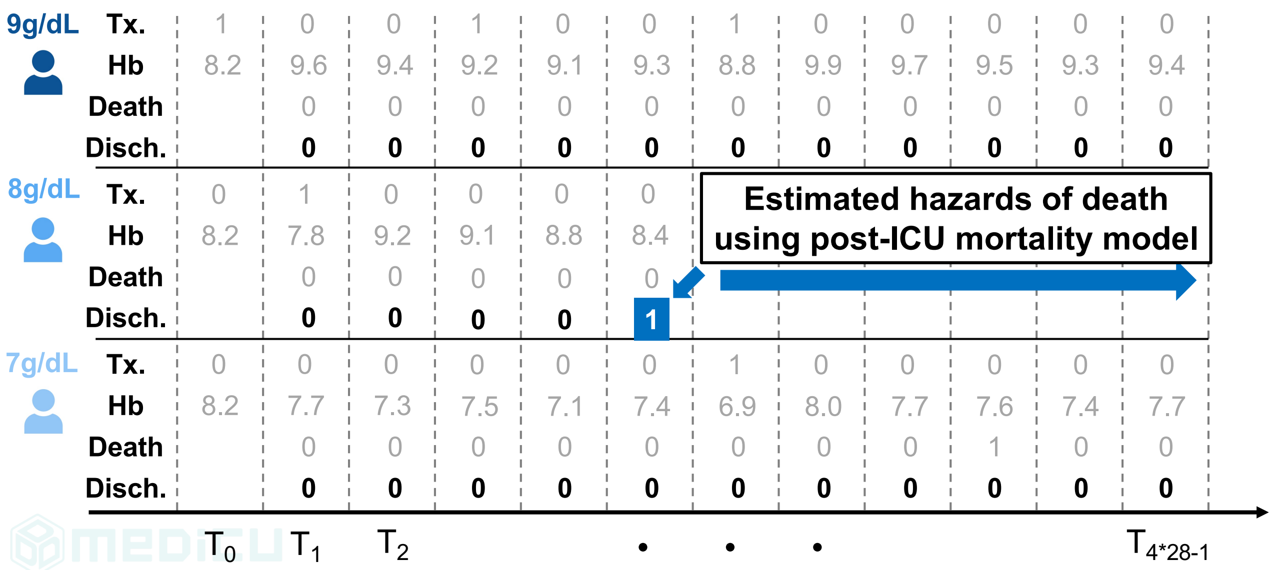
Simulated Event Occurrence Using a Bernoulli Distribution

9g/dL	Tx.	1	0	0	1	0	0	1	0	0	0	0	0
	Hb	8.2	9.6	9.4	9.2	9.1	9.3	8.8	9.9	9.7	9.5	9.3	9.4
	Death		0	0	0	0	0	0	0	0	0	0	0
	Disch.		0	0	0	0	0	0	0	0	0	0	0
8g/dL	Tx.	0	1	0	0	0	0	0	0	1	0	0	0
	Hb	8.2	7.8	9.2	9.1	8.8	8.4	8.6	8.1	7.6	9.2	8.8	8.9
	Death		0	0	0	0	0	0	0	0	0	0	0
	Disch.		0	0	0	0	1	0	0	0	0	0	0
7g/dL	Tx.	0	0	0	0	0	0	1	0	0	0	0	0
	Hb	8.2	7.7	7.3	7.5	7.1	7.4	6.9	8.0	7.7	7.6	7.4	7.7
	Death		0	0	0	0	0	0	0	0	1	0	0
	Disch.		0	0	0	0	0	0	0	0	0	0	0
		T_0	T_1	T_2			•	•	•				T_{4*28-1}

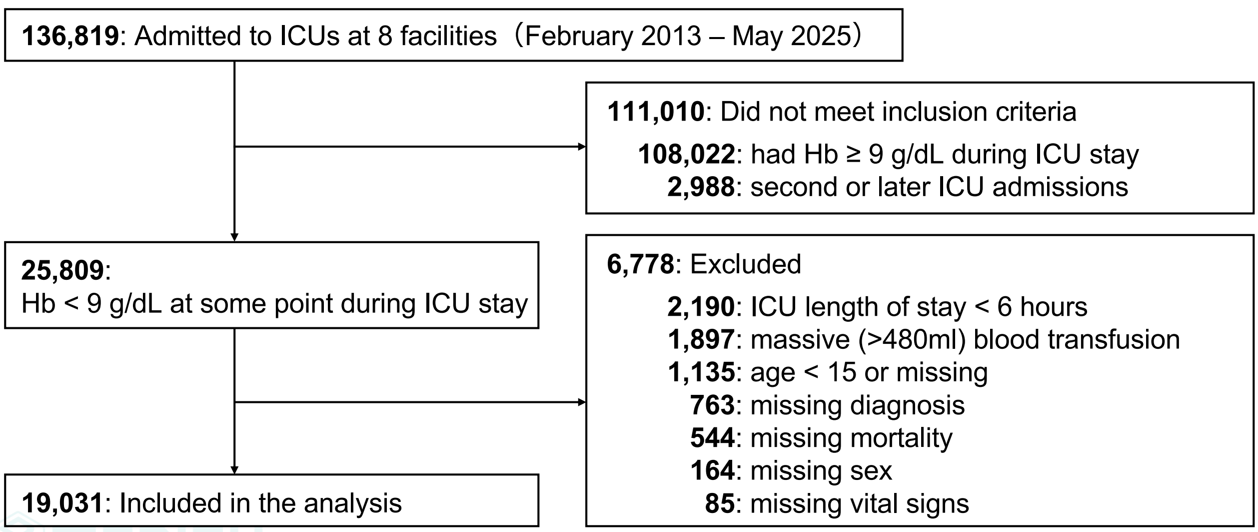
Simulated Event Occurrence Using a Bernoulli Distribution

9g/dL	Tx.	1	0	0	1	0	0	1	0	0	0	0	0
	Hb	8.2	9.6	9.4	9.2	9.1	9.3	8.8	9.9	9.7	9.5	9.3	9.4
	Death		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Disch.		0	0	0	0	0	0	0	0	0	0	0
8g/dL	Tx.	0	1	0	0	0	0	0	0	1	0	0	0
	Hb	8.2	7.8	9.2	9.1	8.8	8.4	8.6	8.1	7.6	9.2	8.8	8.9
	Death		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Disch.		0	0	0	0	1	0	0	0	0	0	0
7g/dL	Tx.	0	0	0	0	0	0	1	0	0	0	0	0
	Hb	8.2	7.7	7.3	7.5	7.1	7.4	6.9	8.0	7.7	7.6	7.4	7.7
	Death		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**
	Disch.		0	0	0	0	0	0	0	0	0	0	0
		T_0	T_1	T_2			•	•	•				T_{4*28-1}

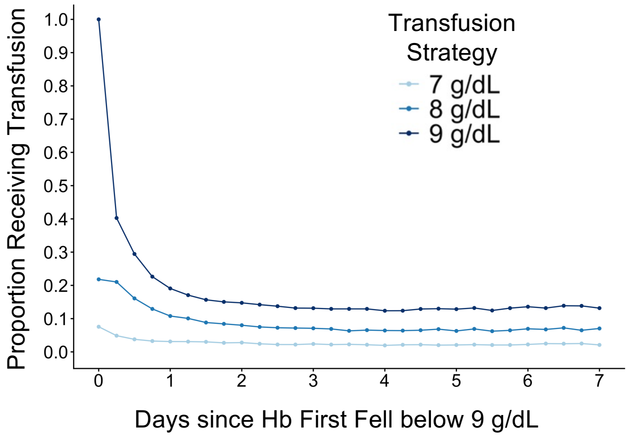
Simulated Post-ICU Mortality for Cases Discharged Alive

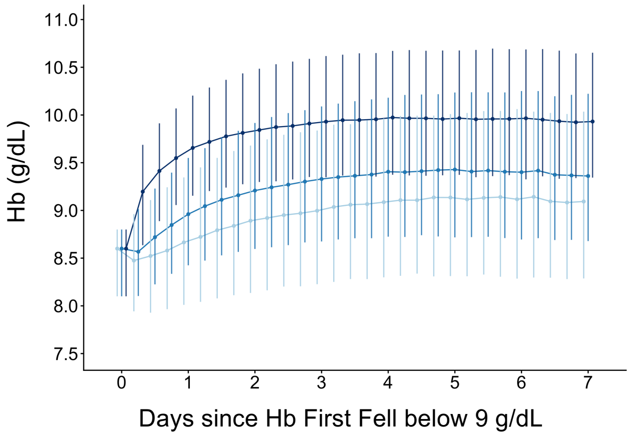


Results：Patient Flow Diagram

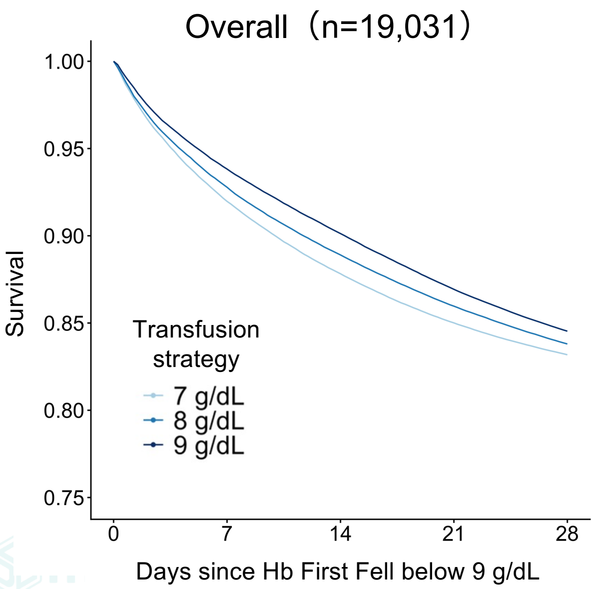


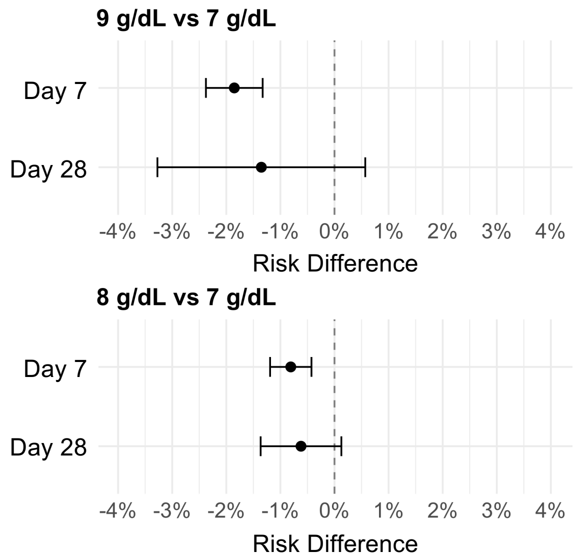
Restrictive Strategy (7g/dL): Fewer Transfusions and Lower Hb



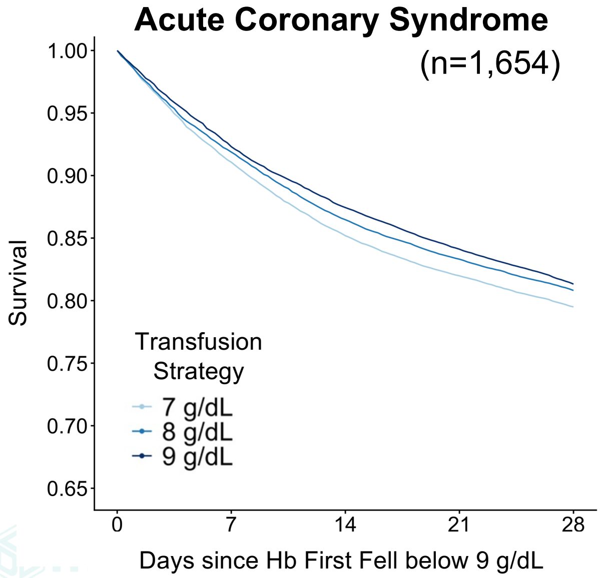


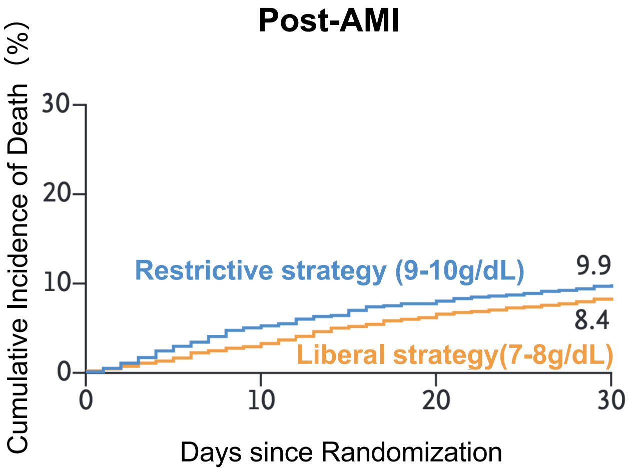
Restrictive Strategy: Lower Survival at Day 7 (Similar at Day 28)





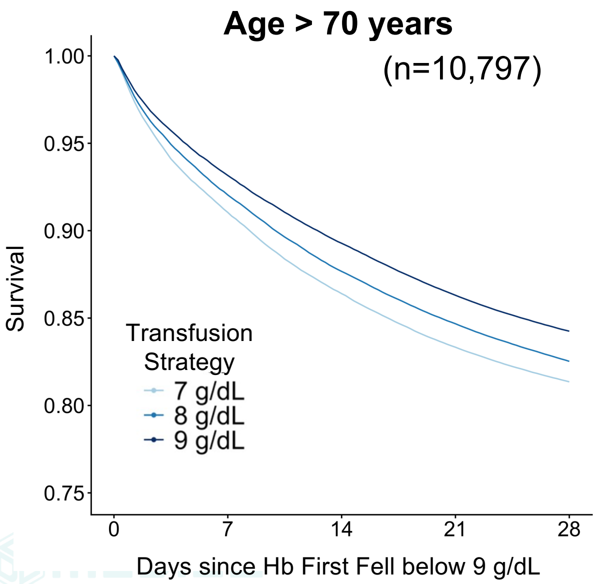
Liberal Strategy Better in Acute Coronary Syndrome: Consistent with a Recent RCT

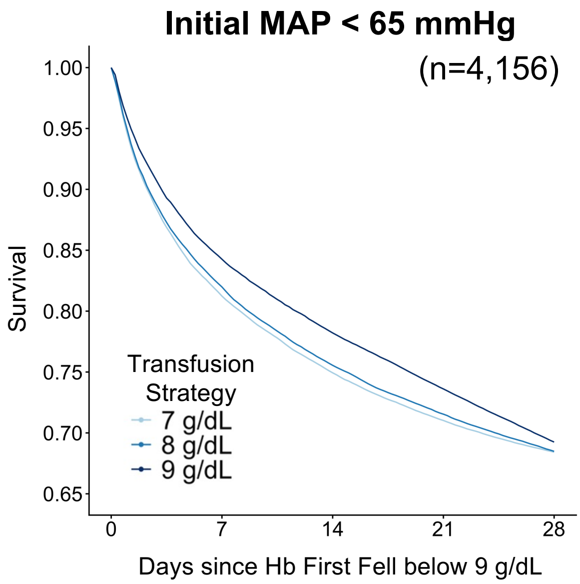




N Engl J Med. 2023;389:2446-2456.

Liberal Strategy Better in Older or Hypotensive Patients





Why we observed different results from early RCTs?

Problems in previous RCTs

- Low adherence (>20% protocol violation) might bias the effect of the liberal strategy toward the null

N Engl J Med. 2014;371:1381-91

Strength of our study

- Our target trial emulation framework using the g-formula allowed us to estimate **per-protocol effects** assuming complete adherence

Measures to Address Limitations

Potential unmeasured confounders

- Extracted a wide range of hemodynamic variables that could influence both outcomes and transfusion decisions

Unavailable post-ICU variables

- Extended the hazard estimation into the post-ICU period, incorporating time-fixed cumulative transfusions during the ICU stay

Conclusion

Compared with a restrictive transfusion strategy (7g/dL), **a liberal transfusion strategy (9g/dL) may reduce early mortality** in ACS, older adults, and hypotensive patients