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Stress hyperglycemia identifies a high-mortality phenotype within lower triglyceride-glucose levels in critically ill adults: a MIMIC-IV landmark cohort study

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Abstract

Background.

The triglyceride-glucose (TyG) index is widely applied to stratify metabolic risk in critically ill patients, but it indexes chronic insulin resistance and may not capture the acute glycemic stress that dominates short-term outcome. We asked whether, among patients in the lower half of the TyG distribution, the stress-hyperglycemia ratio (SHR) identifies a distinct high-risk phenotype.

Methods.

We studied adults in MIMIC-IV at their first ICU stay in whom TyG and SHR were computable from clinically obtained triglycerides, glucose and HbA1c within ± 24 h of admission (N = 3,877 after a 24-hour landmark; N = 3,855 in adjusted models). The primary outcome was 28-day all-cause mortality. Patients were cross-classified by median TyG and median SHR; discordance was also modeled continuously (percentile-rank difference; SHR residualized on TyG, linear and spline). Because SHR contains glucose in its numerator, relative glycemia was additionally examined with a decoupled parameterization entering log glucose and log HbA1c-estimated average glucose (eAG) separately, with collinearity diagnostics. Prespecified analyses included additive and multiplicative interaction, inverse-probability-of-being-measured weighting, and competing-risk analysis of incident acute kidney injury (AKI).

Results.

Among the 1,938 patients in the lower half of the TyG distribution, 28-day mortality was 18.0% with high SHR versus 11.2% with low SHR (adjusted hazard ratio [HR] 1.62, 95% CI 1.26–2.07). This group contained 131 deaths — 23.5% of all 28-day deaths — and its mortality exceeded that of all patients in the upper half of the TyG distribution (18.0% vs 15.0%) at similar SAPS-II (32.1 vs 31.9). It was largely non-diabetic (89.1% without diagnosed diabetes), with normal HbA1c (5.5%) and admission glucose that would not trigger conventional thresholds (median 134 mg/dL; 60% below 140 mg/dL). The gradient tracked SHR rather than TyG (per-SD HR 1.18 vs 1.03 [ns]). In the decoupled model, higher log glucose was associated with higher mortality (1.33, 1.19–1.48) and higher log eAG with lower mortality (0.84, 0.73–0.96), supporting a contribution from glycemia relative to the HbA1c-estimated baseline; collinearity was modest (variance inflation 2.5–3.1; condition number 5.4). Results did not depend on the median split (continuous discordance per SD 1.24, 1.13–1.36) and were unchanged after excluding anemia and chronic kidney disease (1.68, 1.25–2.26). An unmeasured confounder would need a risk ratio of 2.13 to explain the association away. TyG×SHR interaction was null on both scales; incident AKI did not differ across groups; the apparent C-index was 0.766 for the clinical base model and 0.772 after adding the four-category TyG–SHR phenotype.

Conclusions.

Within the lower half of the TyG distribution there exists a high-mortality phenotype defined by relative rather than absolute hyperglycemia, which is not apparent from TyG rank, HbA1c or a conventional glucose threshold alone. These are prognostic observations from a single database that identify a group for earlier risk recognition and trial enrichment rather than a treatment target.

1. Introduction

The triglyceride-glucose (TyG) index [ln(triglyceride×glucose/2)], a simple surrogate of insulin resistance[1], has become one of the most frequently applied metabolic risk markers in critical care research. It has been associated with mortality in mixed intensive care unit (ICU) cohorts[2–5] in stroke[6], in sepsis[7, 8], and with acute kidney injury[9, 10], and it is an established cardiovascular risk marker outside the ICU[11, 12]. Where a marker is applied this widely to separate higher- from lower-risk patients, it is worth asking which dimensions of risk it does not represent.

TyG is built from fasting-state biology and indexes chronic insulin resistance. Short-term outcome in critical illness, however, is dominated by the acute neuroendocrine and inflammatory response, of which stress hyperglycemia is a conserved component[13–15]. The stress-hyperglycemia ratio (SHR), which normalizes admission glucose to chronic glycemia estimated from HbA1c[16], captures relative rather than absolute hyperglycemia and predicts mortality across critically ill and cardiovascular populations[17–20]. Because the two indices represent different constructs, a patient can sit low on the TyG distribution while being acutely and severely stressed by SHR.

Relation to prior work. Several prior analyses have combined the two indices, but each within a single clinical condition. In heart failure, a head-to-head comparison reported SHR to be the more robust long-term mortality marker than TyG[21]; in ischemic stroke, an analysis used quartile cross-tables and mediation to suggest that SHR partly transmits the TyG–mortality association[22]; and further single-disease studies have reported the joint or combined predictive value of TyG and SHR for new-onset atrial fibrillation and mortality during sepsis[23], for major adverse cardio-cerebral events in multivessel coronary artery disease[24], and for all-cause mortality in intracerebral hemorrhage[25]. Across these studies the two indices are treated as competing or additive predictors within a diagnosis; none asks, in an all-comers critical-care population, whether one index systematically fails to represent a dimension of risk that the other captures. Our aim is therefore not to add a further demonstration that one index outperforms the other, nor to combine them into a composite score. We ask instead whether the acute relative-glycemia dimension is represented at all by TyG rank: among patients in the lower half of the TyG distribution, is there a subgroup at high risk of dying, what does it look like clinically, and is it visible through routine glycemic assessment? Answering this requires an all-comers rather than a single-disease cohort, a formal test of whether the two axes interact rather than an assumption of synergy or mediation, correction for the selection inherent in which patients have these biomarkers measured, and a test of whether SHR carries information beyond the admission glucose value itself.

In a broad ICU cohort we therefore (i) quantified mortality within the lower half of the TyG distribution according to SHR and characterized the resulting group clinically; (ii) tested whether the joint gradient reflects SHR, TyG, or their interaction; (iii) examined whether the association reflects relative rather than absolute glycemia, using a parameterization that does not place a ratio and its own numerator in the same model; and (iv) assessed robustness to the median split, to conditions that distort HbA1c, to measurement selection, and to unmeasured confounding.

2. Methods

2.1 Data source and cohort

We used MIMIC-IV[26]. Adults (≥ 18 years) at their first ICU stay (one stay per patient) were eligible if triglyceride, chemistry glucose and HbA1c were available within ± 24 h of ICU admission such that both TyG and SHR were computable. The cohort is therefore defined by availability of glucometabolic biomarkers and is not restricted to any specific diagnosis; inferences apply to patients in whom these tests were clinically obtained. eICU-CRD lacks HbA1c and cannot reproduce SHR; it was used only for a directional TyG-alone comparison, not as external validation.

2.2 Time zero and landmark

To avoid immortal-time and future-information bias arising from the ± 24 h exposure window, time zero was set at a 24-hour landmark: all exposure and adjustment variables were measured no later than 24 h and follow-up began thereafter[27, 28]. Patients who died or left the ICU before 24 h were excluded from the primary analysis. Twenty-eight-day mortality was defined among 24-hour survivors as death from the landmark through ICU-admission day 28.

2.3 Exposure

A single index glucose (the chemistry glucose nearest to ICU admission within ± 24 h) was used for both indices; index triglyceride and HbA1c were taken analogously. TyG = ln(TG[mg/dL]×glucose[mg/dL]/2); SHR = index glucose/(28.7×HbA1c[%] − 46.7), the denominator being the HbA1c-estimated average glucose (eAG). SHR is interpreted as an estimated relative stress-hyperglycemia marker, since HbA1c approximates but is not the pre-illness baseline. High and low TyG and SHR denote position relative to the cohort median; these are distributional descriptors, not validated clinical thresholds. The principal contrast was high versus low SHR within the lower half of the TyG distribution; the full four-group cross-classification, tertiles, and two continuous formulations of discordance were also analyzed.

2.4 Outcomes

The primary outcome was 28-day all-cause mortality. Prespecified secondary outcomes were incident KDIGO AKI[29] after the landmark through day 7, restricted to patients without AKI by 24 h and without baseline end-stage renal disease, with death as a competing event; and 90- and 365-day mortality.

2.5 Covariates

Age, sex, race, SAPS-II, APS-III, first-day SOFA, baseline creatinine, hemoglobin, white blood cell count, diabetes status, Charlson comorbidities, and 24-hour vasopressor, mechanical-ventilation and insulin exposure. The fully adjusted model (M3) comprises age, sex, SAPS-II, diabetes, congestive heart failure, prior myocardial infarction, chronic kidney disease, baseline creatinine and the three 24-hour treatment indicators; adjusted models were fitted on N = 3,855 owing to missing baseline creatinine (< 1%). Body-mass index (58% missing) and lactate (69% missing) were not used in primary adjustment and were imputed only in a multiple-imputation sensitivity analysis.

2.6 Statistical analysis

Cox proportional-hazards models estimated hazard ratios with a stepwise adjustment chain (M0 crude; M2 + severity and comorbidity; M3 fully adjusted). Proportional hazards were assessed by Schoenfeld residual tests, reported globally and per covariate. Interaction was tested on the multiplicative scale and the additive scale (RERI, AP, SI with 400-sample bootstrap confidence intervals)[30]. Selection by measurement was addressed with stabilized, truncated inverse-probability-of-being-measured weights derived from the full first-ICU source population[31]. Incident AKI used cause-specific Cox regression and Aalen–Johansen cumulative incidence with death competing[32, 33]. A reclassification analysis quantified mortality, adjusted hazard, share of total deaths, and the change in sensitivity and specificity when SHR was added to TyG-based flagging[34–36]. E-values were computed after converting the hazard ratio to an approximate risk ratio using the standard transformation for common outcomes, because 28-day mortality (14.4%) cannot be treated as rare[37].

Prespecification and analyses added after initial submission. The frozen cohort, 24-hour landmark, TyG and SHR definitions, median cut-points, M3 covariate set and 28-day mortality outcome were specified before outcome modeling and were not altered at any point. The interpretation presented here was formed after observing those prespecified results. Following an initial submission that was declined by the editor without external review, we added analyses to address methodological objections we anticipated; none changed the cohort, exposure, outcome, landmark or adjustment set. Their prespecification status differs and is stated explicitly: the HbA1c-validity exclusions had a prespecified basis in the analysis protocol and were executed in this round; the comparison of SHR against absolute glucose was foreshadowed by the protocol's component analyses but its present parameterization is new; and the percentile-rank and residual formulations of discordance, the E-value, and the detailed glucometabolic characterization of the low-TyG/high-SHR group are post hoc. A summary is provided in the Supplementary Material.

This study used de-identified public data and was exempt from institutional review.

3. Results

3.1 Cohort

Of 65,366 adult first-ICU patients, 4,625 had both indices computable; after landmark exclusion the analytic cohort comprised 3,877 patients, among whom 557 (14.4%) died within 28 days (Fig. 1). The four groups defined by median TyG (8.814) and median SHR (1.050) contained 1,210, 728, 728 and 1,211 patients (Table 1). TyG and SHR were only weakly correlated (Spearman $\rho = 0.35$; TyG explained 16% of the variance in SHR), so discordant positions on the two axes are common rather than marginal.

Table 1
Baseline characteristics and outcomes by TyG–SHR group (N = 3,877)

Characteristic	Overall	low TyG/low SHR (n = 1210)	low TyG/high SHR (n = 728)	high TyG/low SHR (n = 728)	high TyG/high SHR (n = 1211)
Age, y	68.5 ± 15.3	71.3 ± 15.6	69.8 ± 15.7	65.3 ± 15.2	66.9 ± 14.4
Male, n (%)	2145 (55.3)	644 (53.2)	398 (54.7)	421 (57.8)	682 (56.3)
SAPS-II	31.6 ± 11.9	30.9 ± 11.0	32.1 ± 11.0	28.6 ± 11.1	33.9 ± 13.3
APS-III	36.8 ± 16.8	34.0 ± 15.0	36.9 ± 15.4	33.2 ± 14.0	41.8 ± 19.4
SOFA	3.1 ± 2.7	2.7 ± 2.3	3.2 ± 2.5	2.6 ± 2.3	3.8 ± 3.2
Creatinine, mg/dL	1.1 ± 1.0	1.0 ± 1.0	1.0 ± 0.7	1.1 ± 0.8	1.2 ± 1.1
Hemoglobin, g/dL	11.9 ± 2.2	11.9 ± 2.1	11.6 ± 2.2	12.3 ± 2.1	11.7 ± 2.3
TyG	8.9 ± 0.8	8.3 ± 0.3	8.4 ± 0.3	9.4 ± 0.6	9.6 ± 0.7
SHR	1.1 ± 0.4	0.9 ± 0.1	1.3 ± 0.2	0.9 ± 0.1	1.5 ± 0.5
Index glucose, mg/dL	151.4 ± 87.5	103.1 ± 20.5	139.4 ± 31.0	133.1 ± 47.6	217.7 ± 123.0
HbA1c, %	6.3 ± 1.7	5.9 ± 0.9	5.5 ± 0.6	7.1 ± 2.2	6.7 ± 2.0
Triglycerides, mg/dL	148.3 ± 261.2	84.3 ± 26.2	69.8 ± 21.0	242.6 ± 343.0	202.6 ± 361.6
Diabetes, n (%)	1214 (31.3)	225 (18.6)	79 (10.9)	338 (46.4)	572 (47.2)
Heart failure, n (%)	989 (25.5)	278 (23.0)	186 (25.5)	137 (18.8)	388 (32.0)
Prior MI, n (%)	998 (25.7)	199 (16.4)	191 (26.2)	166 (22.8)	442 (36.5)
CKD, n (%)	616 (15.9)	181 (15.0)	88 (12.1)	97 (13.3)	250 (20.6)
Vasopressor 24 h, n (%)	457 (11.8)	100 (8.3)	95 (13.0)	68 (9.3)	194 (16.0)

Mean ± SD unless stated. High and low denote position relative to the cohort median (TyG 8.814; SHR 1.050). All P < 0.001 except male sex (P = 0.20). Body-mass index and lactate were substantially missing (58% and 69%) and are reported in the Supplementary Material.

Characteristic	Overall	low TyG/low SHR (n = 1210)	low TyG/high SHR (n = 728)	high TyG/low SHR (n = 728)	high TyG/high SHR (n = 1211)
Ventilation 24 h, n (%)	952 (24.6)	193 (16.0)	181 (24.9)	170 (23.4)	408 (33.7)
Insulin 24 h, n (%)	794 (20.5)	105 (8.7)	87 (12.0)	163 (22.4)	439 (36.3)
28-day death, n (%)	557 (14.4)	136 (11.2)	131 (18.0)	61 (8.4)	229 (18.9)
90-day death, n (%)	710 (18.3)	183 (15.1)	165 (22.7)	91 (12.5)	271 (22.4)
365-day death, n (%)	913 (23.5)	255 (21.1)	205 (28.2)	122 (16.8)	331 (27.3)

Mean ± SD unless stated. High and low denote position relative to the cohort median (TyG 8.814; SHR 1.050). All P < 0.001 except male sex (P = 0.20). Body-mass index and lactate were substantially missing (58% and 69%) and are reported in the Supplementary Material.

3.2 A high-mortality group within the lower half of the TyG distribution

The four-group Cox model estimates are presented in Table 2. Among the 1,938 patients in the lower half of the TyG distribution, 28-day mortality was 18.0% in those with high SHR versus 11.2% in those with low SHR (adjusted HR 1.62, 95% CI 1.26–2.07; Table 3, Fig. 2A). This group contained 131 deaths, 23.5% of all 28-day deaths in the cohort. Flagging on high TyG alone would identify 52% of deaths; adding high SHR raises this to 76% (Fig. 2B), necessarily with lower specificity (categorical net reclassification + 0.235 for events, − 0.180 for non-events, net + 0.055). Mortality in the low-TyG/high-SHR group (18.0%) exceeded that of all patients in the upper half of the TyG distribution (15.0%; Fig. 2C). This group is not identified by TyG rank alone; high and low denote position relative to the cohort median rather than a validated clinical threshold.

Table 2
28-day mortality by TyG–SHR group (Cox models; reference = low TyG/low SHR)

Group	M0 crude	M2 + severity/comorbidity	M3 fully adjusted
low TyG/high SHR	1.67 (1.32–2.13)	1.71 (1.34–2.18)	1.57 (1.23–2.00)
high TyG/low SHR	0.74 (0.54–1.00)	0.94 (0.69–1.28)	0.81 (0.60–1.11)
high TyG/high SHR	1.77 (1.43–2.19)	1.67 (1.32–2.10)	1.44 (1.14–1.82)

M3 adjusts for age, sex, SAPS-II, diabetes, heart failure, prior myocardial infarction, chronic kidney disease, baseline creatinine, and 24-hour vasopressor, ventilation and insulin exposure (N = 3,855). Schoenfeld tests for the three exposure terms: p = 0.56, 0.85, 0.64.

Table 3
The high-mortality group within the lower half of the TyG distribution

Metric	Value
Patients in the lower half of the TyG distribution	1,938
28-day mortality, high vs low SHR within this stratum	18.0% vs 11.2%
Adjusted hazard ratio, high vs low SHR (M3)	1.62 (1.26–2.07), p < 0.001
Deaths in the low-TyG/high-SHR group	131 (23.5% of all 28-day deaths)
Sensitivity for 28-day death, TyG alone → TyG + SHR	52.1% → 75.6%
Mortality, low-TyG/high-SHR vs upper half of TyG distribution	18.0% vs 15.0%
Categorical NRI adding SHR (events / non-events / net)	+ 0.235 / −0.180 / net + 0.055
— Clinical profile of this group —	
Diabetes	10.9% (vs 46.9% in high TyG)
HbA1c, mean	5.5%
Index glucose, median	134 mg/dL
Index glucose < 140 / <180 mg/dL	59.6% / 91.5%
SAPS-II	32.1 (vs 31.9 in high TyG)

High and low denote position relative to the cohort median, not validated clinical thresholds; the sensitivity gain is necessarily accompanied by lower specificity. An estimate of 1.64 (1.30–2.07) reported in an earlier version of this analysis arose from a reduced covariate set with an L2 penalty; the fully adjusted M3 estimate is reported here.

3.3 The group is not apparent on routine glycemic assessment

Clinically, this group was largely non-diabetic (diabetes prevalence, 10.9% versus 46.9% among high-TyG patients), with normal HbA1c (mean 5.5%) and admission glucose that would not trigger conventional thresholds: median 134 mg/dL, with 60% below 140 mg/dL and 91.5% below 180 mg/dL (Fig. 3A, Table 3). Illness severity was similar to that of the high-TyG group (SAPS-II 32.1 versus 31.9), so the excess mortality is not explained by a difference in this severity score. The abnormality becomes apparent only when admission glucose is read against the patient's own HbA1c-estimated baseline.

3.4 Relative rather than absolute glycemia

Across the whole cohort the gradient followed SHR rather than TyG (per-SD HR 1.18, 1.11–1.26 versus 1.03, 0.93–1.14; in the same model, SHR 1.19 and TyG 0.97). Absolute index glucose was associated with mortality when modeled alone (per-SD HR 1.14, 1.05–1.23); entered together with SHR, SHR retained its association (1.22, 1.09–1.35) while glucose did not (0.96, 0.84–1.10). Because glucose is

the numerator of SHR, that model contains two mathematically coupled coordinates and its coefficients should not be read as independent effects; collinearity was nevertheless modest (Pearson r = 0.71; variance inflation 2.47 for SHR and 3.09 for glucose; design condition number 5.4). We therefore also fitted a decoupled parameterization entering log glucose and log eAG separately, which represents the same information without including a ratio alongside its own numerator: higher log glucose was associated with higher mortality (per-SD HR 1.33, 1.19–1.48) and higher log eAG with lower mortality (0.84, 0.73–0.96), and the residual of log glucose on log eAG — a direct index of deviation from the estimated chronic baseline — carried an HR of 1.25 (1.15–1.36) per SD (Table 4, Fig. 3B). Together these support, without uniquely proving, a contribution from glycemia relative to the HbA1c-estimated baseline rather than from the absolute value alone. Adjusting the four-group contrasts for index glucose left the low-TyG/high-SHR estimate essentially unchanged (1.52, 1.19–1.94). Within the lower-TyG stratum, additional conditioning on absolute glucose attenuated the estimate to 1.36 (95% CI 0.999–1.862; p = 0.051); for the same reason, this is reported as a sensitivity analysis in which the direction is preserved but precision is reduced, not as an independent replication.

Table 4
Relative versus absolute glycemia, and discordance modeled continuously

Analysis	Adjusted HR per + 1 SD (95% CI)	p
SHR, modeled alone	1.18 (1.11–1.26)	< 0.001
Index glucose, modeled alone	1.14 (1.05–1.23)	0.001
SHR, with glucose in the same model †	1.22 (1.09–1.35)	< 0.001
Index glucose, with SHR in the same model †	0.96 (0.84–1.10)	0.54
Decoupled: log index glucose	1.33 (1.19–1.48)	< 0.001
Decoupled: log HbA1c-estimated average glucose (eAG)	0.84 (0.73–0.96)	0.009
Residual of log glucose on log eAG	1.25 (1.15–1.36)	< 0.001
TyG, with SHR in the same model	0.97 (0.88–1.08)	0.62
Discordance: SHR–TyG percentile-rank difference	1.24 (1.13–1.36)	< 0.001
Discordance: SHR residualized on TyG (linear)	1.18 (1.11–1.26)	< 0.001
Discordance: SHR residualized on TyG (restricted cubic spline)	1.18 (1.11–1.26)	< 0.001
low-TyG/high-SHR vs reference, additionally adjusted for glucose	1.52 (1.19–1.94)	< 0.001
Within lower-TyG stratum, additionally adjusted for glucose †	1.36 (0.999–1.862)	0.051

All models use the M3 covariate set. † SHR = glucose/eAG, so models containing both SHR and glucose are mathematically coupled; their coefficients estimate conditional contrasts rather than independent effects and are reported as sensitivity analyses. Collinearity diagnostics for the SHR+glucose model: Pearson r = 0.71, variance inflation 2.47 (SHR) and 3.09 (glucose), design condition number 5.4. TyG explained 16% of the variance in SHR.

3.5 Findings do not depend on the median split, and no synergy is present

Modeled continuously, discordance was associated with mortality: per SD of the percentile-rank difference between SHR and TyG, adjusted HR 1.24 (1.13–1.36); using SHR residualized on TyG, 1.18 (1.11–1.26) with a linear fit and 1.18 (1.11–1.26) with a four-knot restricted cubic spline fit (Table 4). Because TyG explains only 16% of the variance in SHR and is itself weakly associated with mortality, these measures largely reflect variation in SHR that TyG does not capture; they are complementary representations rather than evidence that discordance carries an independent biological effect. Tertile extremes reinforced the pattern (28-day mortality 18.1% versus 6.9%). Multiplicative interaction was null

(HR 1.03, p = 0.86), as were RERI (0.08, − 0.25 to 0.39), AP (0.05) and SI (1.15): the excess risk is SHR-dominant and additive, which argues against combining the indices into a composite score.

3.6 Robustness

The principal estimate was unchanged under inverse-probability-of-being-measured weighting (1.61, 1.18–2.19) and multiple imputation of body-mass index and lactate (1.62, 1.28–2.06). Excluding conditions that distort HbA1c did not attenuate the association: hemoglobin ≥ 9 g/dL, 1.59 (1.22–2.08); hemoglobin ≥ 8 g/dL, 1.54 (1.19–1.99); no chronic kidney disease, 1.57 (1.20–2.07); no end-stage renal disease, 1.57 (1.23–2.01); excluding both anemia and chronic kidney disease, 1.68 (1.25–2.26); additionally excluding baseline creatinine ≥ 2 mg/dL, 1.63 (1.20–2.20) (Table 5). Proportional hazards held for all three exposure terms (Schoenfeld p = 0.56, 0.85 and 0.64); the assumption was violated for congestive heart failure and mechanical ventilation, and stratifying on both left the estimate unchanged (1.56, 1.22–1.99). After converting the hazard ratio to an approximate risk ratio for this common outcome, an unmeasured confounder would need to be associated with both exposure and mortality by a risk ratio of 2.13 (1.63 for the confidence limit) to explain the association away. The high-versus-low SHR association was directionally consistent in the heart failure (HR 1.30), myocardial infarction (HR 1.59), and sepsis (HR 1.33) subgroups. In the overall landmark cohort, the adjusted HR for high versus low SHR was 1.90 (95% CI 1.54–2.33) among patients without diabetes and 1.16 (95% CI 0.86–1.55) among patients with diabetes (P for interaction = 0.017). In an additional analysis restricted to the low-TyG stratum using Model 3 adjustment, the corresponding HRs were 1.90 (95% CI 1.44–2.52) and 0.86 (95% CI 0.47–1.56), respectively. The apparent Harrell's C-index was 0.766 for the clinical base model, 0.771 for the base model plus continuous SHR, and 0.772 for the base model plus the four-category TyG–SHR phenotype (Table 5). The four-group and subgroup hazard ratios are summarized in Fig. 4.

Table 5
Robustness and supportive analyses

Analysis	Result
Inverse-probability-of-being-measured weighting	HR 1.61 (1.18–2.19)
Multiple imputation of BMI and lactate	HR 1.62 (1.28–2.06)
Excluding hemoglobin < 9 g/dL	HR 1.59 (1.22–2.08)
Excluding hemoglobin < 8 g/dL	HR 1.54 (1.19–1.99)
Excluding chronic kidney disease	HR 1.57 (1.20–2.07)
Excluding end-stage renal disease	HR 1.57 (1.23–2.01)
Excluding anemia and chronic kidney disease	HR 1.68 (1.25–2.26)
Additionally excluding baseline creatinine ≥ 2 mg/dL	HR 1.63 (1.20–2.20)
Stratified on covariates violating proportional hazards	HR 1.56 (1.22–1.99)
E-value after HR→RR conversion (point / confidence limit)	2.13 / 1.63
Subgroup: heart failure / myocardial infarction / sepsis	1.30 / 1.59 / 1.33
High versus low SHR by diabetes status in the overall landmark cohort (P for interaction = 0.017)	No diabetes: HR 1.90 (1.54–2.33); diabetes: HR 1.16 (0.86–1.55)
High versus low SHR by diabetes status within low TyG (Model 3)	No diabetes: HR 1.90 (1.44–2.52); diabetes: HR 0.86 (0.47–1.56)
Tertile extremes (mortality)	18.1% vs 6.9%
Additive interaction: RERI / AP / SI	0.08 (− 0.25–0.39) / 0.05 / 1.15 (all null)
Apparent Harrell's C-index by model	Clinical base: 0.766; base + continuous SHR: 0.771; base + four-category TyG–SHR phenotype: 0.772
Incident AKI, cause-specific HR (highest-risk cell)	1.15 (0.98–1.36), null across groups
eICU TyG-alone (no HbA1c; directional only)	per-SD OR 1.22

Unless stated, the reported hazard ratio is for the low-TyG/high-SHR contrast under the M3 covariate set. E-values were computed after converting the hazard ratio to an approximate risk ratio, because 28-day mortality (14.4%) is not a rare outcome. The clinical base model included age, sex, SAPS-II, diabetes, and baseline creatinine. Metabolic terms were added separately to the base model. Harrell's C-indices were calculated in the model-development sample (n = 3,855). The adjustment sets for overall-cohort subgroup analyses are described in Fig. 4. *Diabetes-stratified analyses within low TyG use Model 3 adjustment.*

4. Discussion

In a broad ICU cohort, a high stress-hyperglycemia ratio identified a high-mortality group among patients sitting in the lower half of the triglyceride-glucose distribution. Their 28-day mortality was 18.0% — higher than the 15.0% observed across the entire upper half of the TyG distribution — and they accounted for 23.5% of all early deaths. The finding is best read as evidence that the two indices represent non-equivalent metabolic constructs: TyG rank does not represent the acute relative-glycemia dimension, and a patient can be unremarkable on one axis while carrying substantial risk on the other.

What makes this group clinically consequential is that nothing else about them is conspicuous. Nine in ten have no diagnosed diabetes; their HbA1c averages 5.5%; their admission glucose is median 134 mg/dL, with three in five below 140 mg/dL and more than nine in ten below 180 mg/dL. Their SAPS-II is similar to that of the patients with high TyG. The abnormality is visible only when the admission glucose is read against that patient's own chronic glycemia — a normal-looking glucose in someone whose baseline is genuinely low.

That the signal reflects relative rather than absolute glycemia is supported by two complementary parameterizations. Absolute glucose was associated with mortality alone but not alongside SHR; because those two variables are mathematically coupled, we did not rest the interpretation on that model. In a decoupled model containing log glucose and log HbA1c-estimated average glucose as separate terms, the two moved in opposite directions — higher acute glucose associated with higher mortality, higher chronic baseline with lower mortality — which is what the relative-glycemia construct predicts and which does not depend on placing a ratio beside its own numerator. Relative hyperglycemia has long been argued to be more prognostic than absolute glucose in acute cardiovascular illness[16, 38, 39]. The concentration of the effect in patients without diagnosed diabetes fits the same construct: where chronic glycemia is already high and variable, the denominator is less informative and the relative signal is blunted. Stress hyperglycemia is itself a conserved component of the acute response to critical illness[13–15], and acute hyperglycemia promotes oxidative stress and endothelial dysfunction[40].

Our findings extend rather than repeat the two prior combined analyses. A head-to-head comparison in heart failure concluded that SHR was the more robust long-term marker[21], and a stroke analysis argued that SHR partly transmits the TyG effect[22]. We move from asking which index performs better to asking what the TyG dimension does not represent, in an all-comers population, and we show that the two axes do not interact on either scale — evidence against combining them into a composite. The practical implication differs accordingly: the value of SHR here is not that it improves global discrimination, which it does only modestly, but that it redistributes which patients are flagged, identifying a group that carries a quarter of early deaths and sits in the lower half of the TyG distribution.

Several qualifications frame how these results should be used. The median cut-points are distributional descriptors and phenotype-discovery tools, not deployable thresholds, and TyG itself was not associated with 28-day mortality in this cohort, so "lower TyG" denotes position in a distribution rather than classification by a validated rule; correspondingly, these data do not demonstrate that any deployed TyG-

based clinical rule misclassifies patients. The gain in global discrimination over a clinical model was small; this is risk recognition, not a validated prediction rule. Identifying a high-risk stress-hyperglycemia group does not imply that lowering glucose helps, as trials of intensive glucose control in the ICU have shown benefit and harm depending on setting[41, 42], and this observational design cannot address treatment. SHR also requires HbA1c, which is not universally measured.

Strengths include a 24-hour landmark design that removes immortal-time and future-information bias, prespecified testing of additive and multiplicative interaction, inverse-probability-of-being-measured weighting, competing-risk handling of AKI, collinearity diagnostics with a decoupled parameterization for the relative-glycemia question, and stability across continuous formulations of discordance, exclusions for HbA1c-distorting conditions, and stratification for covariates violating proportional hazards.

Limitations. First, both indices are measured in a minority of ICU patients; stabilized measurement weighting left estimates unchanged but addresses observed source-population differences only, so residual selection may persist and inferences apply to patients in whom both indices were clinically obtained. Second, SHR relies on HbA1c as a baseline proxy. Excluding anemia, chronic kidney disease and end-stage renal disease did not attenuate the association, but recent transfusion, hemolysis, hemoglobinopathies, erythropoiesis-stimulating therapy and pregnancy also alter HbA1c and could not be identified reproducibly in these data; we therefore state that results were stable after excluding identifiable anemia and renal dysfunction, not that HbA1c distortion was eliminated. Third, SHR could not be externally validated because eICU-CRD lacks HbA1c, so this remains a single-database study for SHR and discordance; the eICU TyG-alone result is a directional comparison only. Fourth, body-mass index and lactate were substantially missing and residual confounding may persist. Fifth, incident AKI showed no difference across groups; a null association does not exclude other mechanistic pathways.

5. Conclusion

Within the lower half of the triglyceride-glucose distribution — among critically ill patients whose lipid profile, HbA1c and absolute glucose all appear unremarkable — a high stress-hyperglycemia ratio identifies a group whose 28-day mortality exceeds that of patients in the upper half of the TyG distribution and which accounts for nearly a quarter of all early deaths. TyG rank and relative glycemia are non-equivalent metabolic dimensions; these prognostic findings identify a group for earlier risk recognition and for enrichment of future trials, and prospective studies should establish whether acting on this signal changes outcome.

Declarations

Ethics approval and consent to participate. MIMIC-IV and eICU-CRD are de-identified, publicly available databases approved by the institutional review boards of the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology; the requirement for individual consent was waived.

Consent for publication. Not applicable.

Availability of data and materials. MIMIC-IV and eICU-CRD are available from PhysioNet (https://physionet.org) to credentialed users.

Code availability. The analysis code is openly available at Zenodo (https://doi.org/10.5281/zenodo.22986069). Patient-level data are available to credentialed users from PhysioNet under the applicable Data Use Agreements.

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Authors' contributions. L.L. (Liyi Liao): conceptualization, methodology, software, formal analysis, writing – original draft. C.Z. (Cheng Zeng): data curation, investigation, writing – review & editing. P.T. (Peiqi Tang): data curation, validation, writing – review & editing. P.C. (Pengfei Chen): investigation, visualization, writing – review & editing. X.L. (Xuping Li): methodology, validation, writing – review & editing. X.H. (Xinqun Hu): conceptualization, supervision, project administration, writing – review & editing, and is the guarantor. All authors interpreted the results, critically revised the manuscript, and approved the final version.

Reporting. Reported in accordance with the STROBE statement[43]; a completed checklist is provided as Supplementary Material.

Supplementary material. Supplementary Figures S1–S4 (TyG–SHR joint distribution and group-specific mortality; index-glucose density by group; Aalen–Johansen cumulative incidence of AKI with death competing; restricted cubic spline of SHR versus 28-day mortality), Supplementary Tables S1–S2 (full baseline including body-mass index and lactate; prespecification status of each analysis), and the STROBE checklist are provided in the Supplementary Material.

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Figures

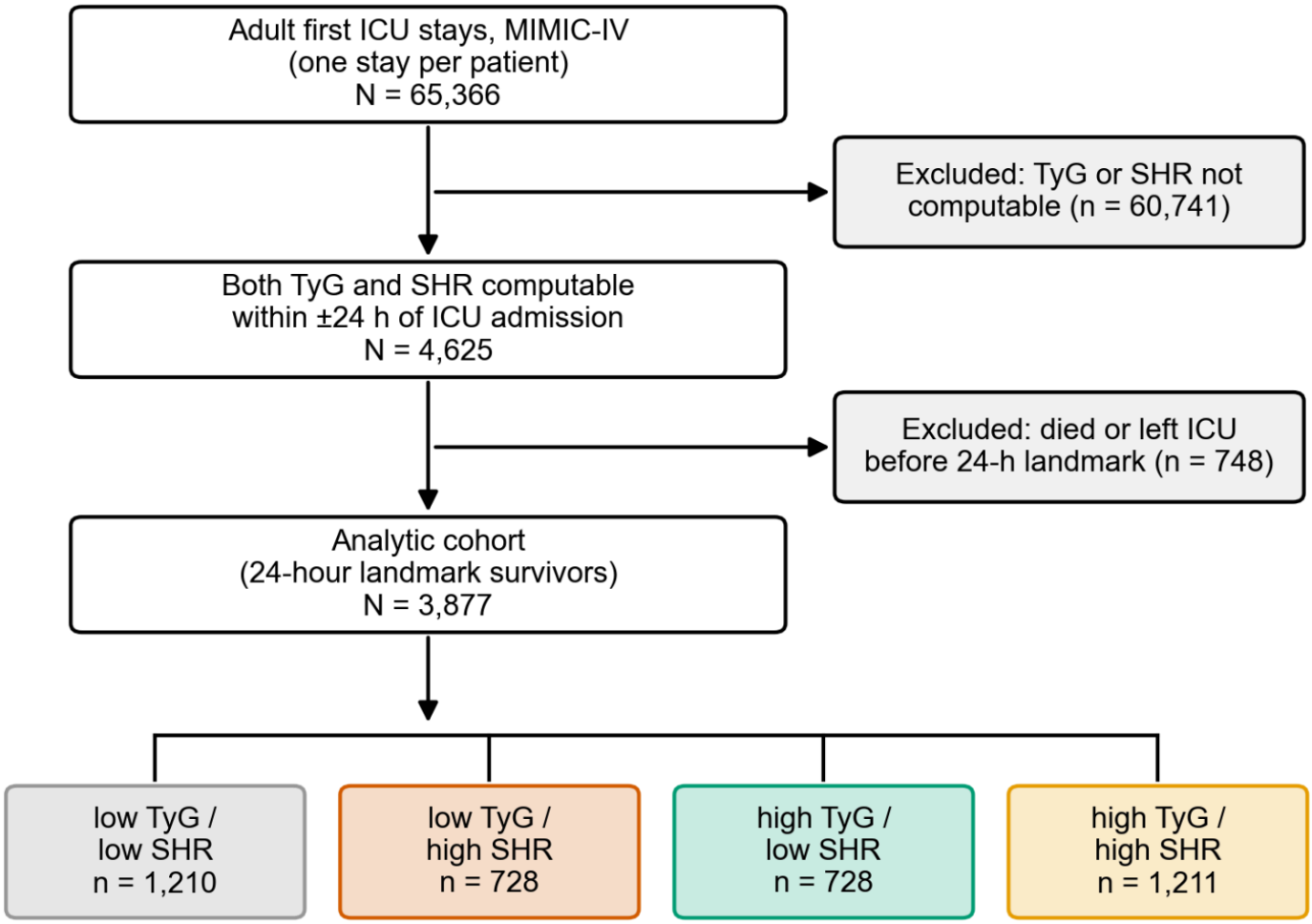


Figure 1

Cohort flow. The analytic cohort is defined by availability of clinically obtained triglycerides, glucose and HbA1c, and is restricted to 24-hour survivors by the landmark design.

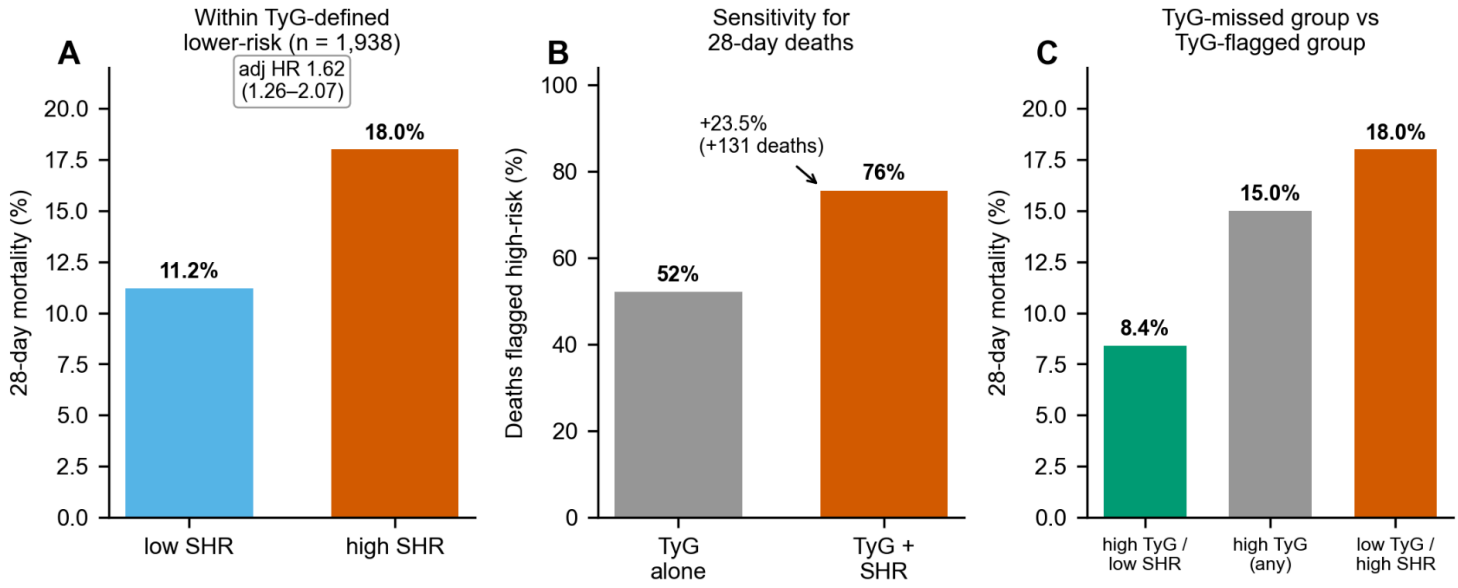


Figure 2

(A) 28-day mortality by SHR within the lower half of the TyG distribution. (B) Sensitivity for 28-day deaths, TyG alone versus TyG+SHR. (C) Mortality of the low-TyG/high-SHR group compared with all patients in the upper half of the TyG distribution. High and low denote position relative to the cohort median.

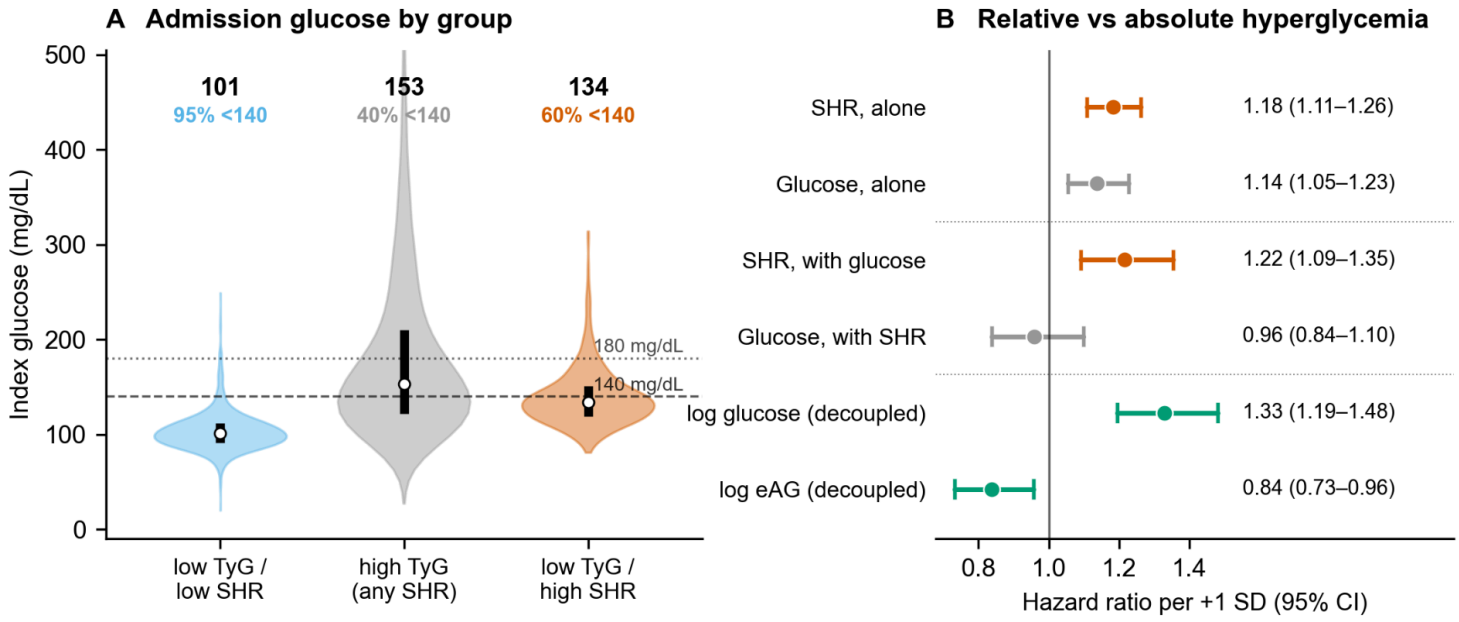


Figure 3

(A) Distribution of admission glucose by group, with 140 and 180 mg/dL reference lines. (B) Hazard ratios per +1 SD for SHR and absolute glucose modeled alone and together, and for the decoupled parameterization entering log glucose and log HbA1c-estimated average glucose (eAG) separately. eAG, estimated average glucose.

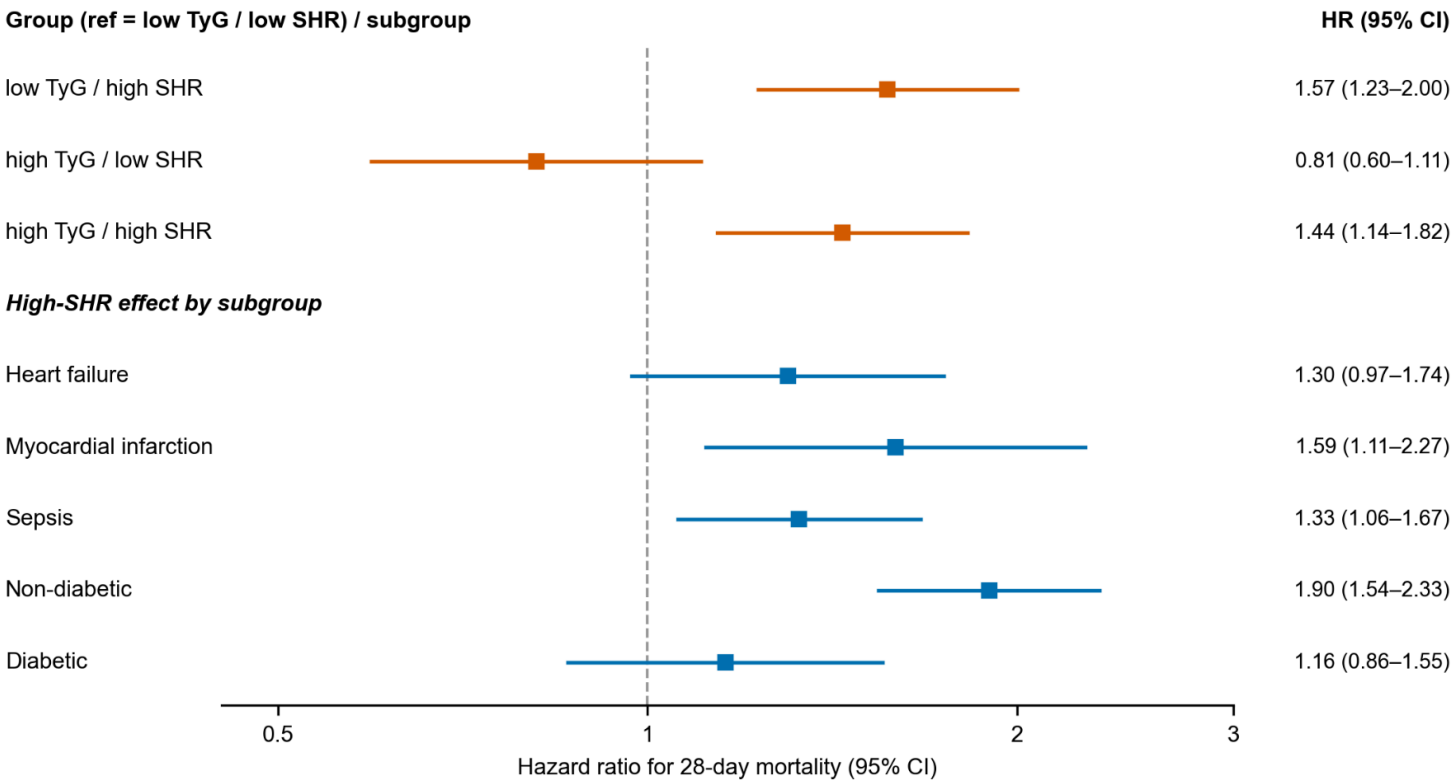


Figure 4

Adjusted hazard ratios for 28-day mortality in the four-group and subgroup analyses. Four-group estimates use Model 3, with low TyG/low SHR as the reference. Subgroup estimates compare high versus low SHR and adjust for age, sex, and SAPS-II; diabetes-stratified estimates additionally adjust for baseline creatinine. Subgroup models used L2 penalties of 0.02 for the heart failure, myocardial infarction, and sepsis analyses and 0.01 for the diabetes-stratified analyses.

Supplementary Files

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- FigureS12x2grid.tiff
- FigureS3akicif.tiff
- FigureS4shrrcs.tiff
- STROBEchecklistLHD.docx
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