

Whole-Cardiac-Cycle ECG Dynamics in Critical Illness: The Spatial QRS- T Angle as a Prognostic Marker, an Early-Warning Signal for Arrhythmia and Myocardial Injury, and an In-Vivo Pharmacodynamic Readout

Ye Hui

Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine

Zhang Qian

Shanghai Pudong New Area People's Hospital, Shanghai Jiao Tong University School of Medicine

Chen Song

Shanghai Pudong New Area People's Hospital, Shanghai Jiao Tong University School of Medicine

Li Peiwu

Shanghai Pudong New Area People's Hospital, Shanghai Jiao Tong University School of Medicine

Wan Jian

Shanghai Pudong New Area People's Hospital, Shanghai Jiao Tong University School of Medicine

Yilong Hao

haoyilong@126.com

Shanghai Pudong New Area People's Hospital, Shanghai Jiao Tong University School of Medicine

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Abstract

Background. Electrocardiographic prediction in critical illness has relied on single parameters measured once — most often the corrected QT interval — with modest and inconsistent results. Whether quantitative parameters spanning the whole cardiac cycle (depolarization through repolarization), measured from every ECG of an ICU stay, carry independent prognostic and mechanistic information is unknown.

Methods. We linked MIMIC-IV v3.1 to the MIMIC-IV-ECG waveform subset and built a cohort of 14,319 adult ICU stays without known coronary artery disease, atrial fibrillation, or pacing (25,112 analyzable ECGs from a 72,166-ECG linked pool). We assembled a whole-cycle parameter panel per ECG: machine-derived intervals and axes (heart rate, PR, QRS duration, QT/QTc, frontal QRS-T angle) and waveform-measured amplitudes from a validated median-beat engine (ST amplitude, J-to-Tpeak amplitude, QRS voltage, ST-T area, Tp-Te). Analyses: (1) 48-hour landmark Cox models for 28-day mortality; (2) linear mixed models of day-by-day trajectories by survival; (3) new-onset repolarization abnormalities as exposures for ECG-specific outcomes (new atrial tachyarrhythmia, new myocardial injury) with cause-specific and Fine–Gray models; (4) within-patient difference-in-differences ECG responses to ICU interventions, with amiodarone as a positive control.

Results. The spatial QRS-T angle was the strongest whole-cycle predictor of 28-day mortality: per-SD HR 1.125 (95% CI 1.068–1.185; $P < 0.0001$) for the 48-h maximum, with dose-response across strata (90° – 120° vs $< 60^{\circ}$: HR 1.23; $\geq 120^{\circ}$: HR 1.35), independent of age, sex, SOFA, lactate, and MAP. QTc was null (HR 0.95; $P = 0.08$), as were QRS duration and T-wave amplitudes; J-to-Tpeak amplitude (HR/SD 1.121; $P < 0.0001$) and low QRS voltage (HR 0.905; $P < 0.01$) added independent signal. Trajectories separated from day 1 (mixed-model survival main effect + 15.3%; $P = 1 \times 10^{-34}$) without subsequent divergence (day $\times$ survival $P = 0.40$), and adding within-stay change to the first ECG gave no incremental discrimination (Δ AUC = 0.0005) — the first ECG carried essentially all prognostic information for mortality. For ECG-specific outcomes, by contrast, new-onset abnormalities were strongly predictive: new-onset ST depression $\rightarrow$ new atrial tachyarrhythmia HR 3.10 (1.51–6.36) and $\rightarrow$ new myocardial injury HR 2.69 (1.32–5.49); new-onset QRS-T angle $\geq 90^{\circ}$ $\rightarrow$ atrial tachyarrhythmia HR 3.77 (2.03–7.01); QTc ≥ 500 ms predicted nothing. In the pharmacodynamic analysis, amiodarone initiation produced the expected + 16.4 ms QTc prolongation ($P = 0.0006$) and – 15.6 bpm heart-rate reduction ($P < 0.0001$), validating the framework; norepinephrine initiation was followed by + 5.7 ms QTc ($P < 0.05$), and renal replacement therapy initiation by + 6.4 ms QTc, + 7.5° QRS-T angle, and + 3.6 ms QRS widening.

Conclusions. In critical illness, spatial depolarization–repolarization mismatch — not repolarization duration — is the dominant ECG prognostic axis. It is measurable from the first ECG, static information suffices for mortality prediction, but new-onset electrical abnormalities precede arrhythmia and myocardial injury with 3–4-fold hazard ratios, and the same panel reads out drug and organ-support effects in vivo. Whole-cycle ECG dynamics are a quantitative, reproducible, and clinically actionable monitoring layer for the ICU.

1. Introduction

The 12-lead ECG is the most frequently repeated quantitative measurement in intensive care, yet ICU prognostication uses it mainly through single, hand-measured parameters — most often the corrected QT interval [1–3] — taken from one tracing. Two limitations follow. First, the ECG encodes the whole cardiac cycle: atrial depolarization (PR), ventricular depolarization (QRS amplitude, duration, axis), and repolarization (ST segment, T-wave amplitude and area, QT, and the spatial angle between the depolarization and repolarization vectors) [4, 5]. Second, the ICU stay generates dozens of ECGs per patient, and the dynamics — new-onset changes against the patient's own baseline — may carry different information than any single value.

Existing evidence is constrained by scale and method. Studies of the QRS-T angle in the general population and in cardiac cohorts establish its prognostic value [6–9], but studies in critical illness are small (largest $n \approx 450$), manually measured, and static [10–12]. Deep-learning ECG mortality scores (e.g., E3A, developed in MIMIC-IV) use the first ECG only [13, 14], leaving open whether longitudinal measurement adds anything — while the broader AI-ECG literature demonstrates how much information standard ECGs carry [15–19]. Vectorcardiographic work in COVID-19 cohorts (MaastrICht, $n = 322$) hinted that global electrical mismatch tracks severity [20, 21], but covered few parameters in one disease at one center.

We used the linked MIMIC-IV / MIMIC-IV-ECG resource — 25,112 analyzable waveform ECGs across 14,319 ICU stays without known structural or ischemic heart disease (from a 72,166-ECG, 35,906-stay linked pool) — to ask three questions: (1) which whole-cycle parameters, measured at scale, predict 28-day mortality, and does longitudinal change add to the first ECG; (2) do new-onset electrical abnormalities predict ECG-specific outcomes (arrhythmia, myocardial injury) better than mortality; and (3) can the same panel serve as an in-vivo pharmacodynamic readout for ICU interventions, using amiodarone as a positive control?

2. Methods

2.1 Cohort

Adult ICU stays in MIMIC-IV v3.1 [22] with ≥ 1 in-stay diagnostic 12-lead ECG from the MIMIC-IV-ECG matched subset [23,24], excluding known coronary artery disease, prior myocardial infarction, PCI/CABG, atrial fibrillation or flutter, and permanent pacing (ICD-9/10 codes): 94,458 adult ICU stays $\rightarrow$ 35,906 with ≥ 1 in-stay ECG (72,166 ECGs) $\rightarrow$ 14,319 stays with 25,112 analyzable ECGs after exclusions; 28-day mortality 13.6% (1,944 deaths). Ethics approval with consent waiver (Pudong New Area People's Hospital); STROBE reporting [25], flow diagram in Supplementary Figure S1.

2.2 Whole-cycle parameter panel

Per ECG: (i) machine-derived (GE Marquette 12SL) heart rate, PR interval, QRS duration, QT and QTc (Bazett/Fridericia), P/QRS/T axes, and the frontal QRS-T angle |QRS axis – T axis| mapped to $[0^\circ, 180^\circ]$ [5]; (ii) waveform-derived from a validated median-beat engine (released with this paper): per-lead median beats constructed after Pan–Tompkins-lite R detection [26] with ectopic-beat rejection (correlation <0.9), automated delineation, and measurement of ST amplitude at J+60 ms vs the PR baseline, J-point-to-T-peak amplitude, QRS peak-to-peak voltage, ST-T area, and Tp-Te interval [5,27]. Engine validation: the engine-corrected ST-depression label yielded the expected association with mortality (HR 1.41) where a mis-anchored implementation yielded noise-level QRS reconstruction and a null result (companion methodological report). Panel coverage is reported in Table 1; engine-corrected ST and amplitude parameters are illustrated in Figure 3.

2.3 Statistical analysis

- (1) Landmark prognosis. 48-h landmark Cox models [28,29] (at-risk $n=11,382$; 1,248 deaths; of these, 11,357 stays with axis data and 1,245 deaths entered the QRS-T angle analyses reported below) per parameter (48-h maximum and mean, per SD), adjusted for age, sex, SOFA, and lactate; QRS-T angle additionally stratified ($<60^\circ/60-90^\circ/90-120^\circ/\geq 120^\circ$).
- (2) Trajectories. Linear mixed models, parameter $\sim \text{day} \times 28\text{-day survival} + (1|\text{stay})$, over ICU days 1–5.
- (3) Dynamic increment. 5-fold cross-validated logistic regression and gradient boosting for 28-day mortality: first-ECG panel vs first + within-stay Δ panel; ΔAUC with bootstrap CI.
- (4) ECG-specific outcomes. Outcomes within 7 days after the 48-h landmark: new atrial tachyarrhythmia (machine-interpreted ECG text, in stays free of atrial arrhythmia before landmark), new ventricular tachycardia, and new myocardial injury (troponin T above the 99th percentile [27] in stays without elevated troponin before landmark). Exposures: any vs new-onset ST depression (≤ -0.10 mV in ≥ 2 contiguous leads), QRS-T angle $\geq 90^\circ$, QTcF ≥ 500 ms, HR ≥ 100 . Cause-specific Cox and Fine–Gray models [29,30] (death as competing event), adjusted as above.
- (5) Pharmacodynamics. For six interventions (amiodarone, magnesium sulfate, norepinephrine, insulin infusion, renal replacement therapy, furosemide), we identified initiation times from infusion/procedure records, paired the last pre-initiation ECG (≤ 48 h before) with the first post-initiation ECG (6–48 h after) within patient, and computed difference-in-differences against time-matched ECG pairs from untreated stays, adjusted for the pre-value.

Two-sided $\alpha=0.05$. All numbers generated programmatically from single results files.

3. Results

3.1 The spatial QRS-T angle, not the QT interval, predicts mortality

In the 48-h landmark cohort (n=11,357 with axis data; 1,245 deaths), the QRS-T angle predicted 28-day mortality per SD (Table 2; Figure 2) (48-h maximum HR 1.125 [1.068–1.185], $P=9\times 10^{-6}$; mean HR 1.125; first ECG HR 1.111 [1.055–1.170]), independent of demographics and severity. The dose-response was graded: versus $<60^\circ$, HR 1.10 (0.93–1.31) for $60\text{--}90^\circ$, 1.23 (1.00–1.50) for $90\text{--}120^\circ$, and 1.35 (1.17–1.56) for $\geq 120^\circ$ ($P=3\times 10^{-5}$). Heart rate carried comparable prognostic weight (48-h max HR/SD 1.239 [1.177–1.305]).

By contrast, QTcF was null (48-h max HR/SD 0.952 [0.901–1.006], $P=0.083$; first ECG 0.941 [0.891–0.994], directionally protective), as were QRS duration (1.033, $P=0.23$), T-wave amplitude, and Tp-Te [31]. PR interval showed a modest inverse association (0.908 [0.854–0.966]). Among waveform amplitudes, J-to-Tpeak amplitude (HR/SD 1.121, $P<0.0001$), low QRS voltage (0.905, $P<0.01$) [32], and ST-T area (0.930, $P<0.01$) were independently associated; corrected ST depression (any within 48 h) carried HR 1.41 (1.23–1.63).

3.2 Trajectories separate at day 1 and do not diverge; the first ECG suffices for mortality

Mixed models (18,369 ECGs, 13,964 stays; Table 2 trajectory panel; Figure 1) showed a large survival main effect for the QRS-T angle ($+15.3^\circ$ in non-survivors; $P=1\times 10^{-34}$) and heart rate ($+9.8$ bpm; $P=4\times 10^{-67}$), but no day $\times$ survival interaction (QRS-T: $+0.42^\circ/\text{day}$, $P=0.40$; HR: $P=0.36$): the groups were already separated on day 1 and remained parallel. Consistently, adding within-stay change to the first-ECG panel gave no incremental discrimination (Table 2 increment panel; Figure 2) (logistic ΔAUC -0.0005 [-0.0016 , $+0.0007$]; gradient boosting ΔAUC -0.003 [-0.007 , -0.0002]). K-means trajectory phenotyping (stays with ≥ 3 daily ECGs; n=666) recovered narrow ($\sim 20\text{--}24^\circ$), intermediate ($\sim 66\text{--}70^\circ$), and wide ($\sim 130\text{--}140^\circ$) phenotypes, but wide-angle patients were underrepresented (142/666) – they died before accumulating three ECGs (survivor bias) – and phenotype membership did not significantly predict mortality (intermediate vs narrow HR 1.41 [0.97–2.04], $P=0.07$; wide vs narrow HR 1.06 [0.70–1.61], $P=0.77$).

3.3 New-onset abnormalities predict arrhythmia and myocardial injury

Where Δ added nothing for mortality, new-onset status was decisive for ECG-specific outcomes (Table 3; Figure 4). After the 48-h landmark, 125 stays developed new atrial tachyarrhythmia, 10 ventricular tachycardia, and 150 new myocardial injury (troponin surveillance was sparse: 530 stays with post-landmark measurement). New-onset atrial arrhythmia and myocardial injury are established markers of adverse prognosis in critical illness [27,33–35]. New-onset ST depression (210 exposed) preceded new atrial tachyarrhythmia (cause-specific HR 3.10 [1.51–6.36], $P=0.002$) and new myocardial injury (HR 2.69 [1.32–5.49], $P=0.007$); any (prevalent) ST depression was weaker (1.82 and 1.42 [NS]), indicating that change against baseline, not presence, signals imminent events. New-onset QRS-T angle $\geq 90^\circ$ (262

exposed) preceded atrial tachyarrhythmia with HR 3.77 (2.03–7.01; $P=3\times 10^{-5}$); prevalent $\geq 90^\circ$ was weaker (1.77). QTcF ≥ 500 ms predicted no outcome. Fine–Gray subdistribution hazards were nearly identical to cause-specific HRs throughout. Composite-outcome results mirrored the components (new-onset ST depression HR 2.61 [1.52–4.47], $P=0.0005$).

3.4 The panel reads out drug and organ-support effects in vivo

Amiodarone (positive control; $n=41$ paired stays; Table 4; Figure 5) produced the expected pharmacodynamics [36]: Δ QTc +16.4 ms [7.0–25.7] ($P=0.0006$) and Δ HR –15.6 bpm ($P<0.0001$) versus untreated matched pairs – validating the within-patient DiD framework. Norepinephrine initiation ($n=245$) was followed by +5.7 ms QTc ($P<0.05$). RRT initiation ($n=180$) was followed by +6.4 ms QTc ($P<0.05$), +7.5° QRS-T angle ($P<0.05$), +3.6 ms QRS widening ($P<0.01$), and –0.06 mV T-wave amplitude ($P<0.01$) – a coherent picture of post-RRT electrical remodeling [37] not attributable to any single electrolyte. Magnesium sulfate and insulin showed no detectable ECG response.

4. Discussion

4.1 Principal findings

Three conclusions emerge. First, spatial depolarization–repolarization mismatch is the dominant ECG prognostic axis in critical illness: the QRS-T angle predicted mortality independently, with dose-response, at 25-fold the sample of prior studies, while the field's favorite parameter – QTc – was null or directionally protective. Second, for mortality the signal is present on arrival and static: trajectories separate by day 1 and run parallel; longitudinal Δ adds nothing. This is good news for translation – one ECG, one angle, no tracking infrastructure – and it reframes deep-learning ECG scores: their headroom lies in what they read, not how often. Third, for events rather than fate, new-onset change is everything: new ST depression and new QRS-T widening preceded arrhythmia and myocardial injury with 3–4-fold hazards while prevalent abnormalities were weak and QTc was silent. Electrical instability is an early-warning layer, not a mortality score.

4.2 Mechanistic interpretation

The QRS-T angle integrates ventricular conduction, regional repolarization heterogeneity, and loading conditions into a single spatial metric [4, 9, 38]; widening reflects loss of the normal concordance between depolarization and repolarization wavefronts. That it – rather than repolarization duration – tracks ICU mortality suggests the lethal substrate is heterogeneity (ischemia without known CAD, dyssynchrony, metabolic and inflammatory remodeling), not delay. The post-RRT signature (QTc + QRS widening + angle widening + T-amplitude loss) is consistent with rapid shifts in volume, potassium, calcium, and acid–base acting on both depolarization and repolarization [37], and illustrates the panel's use as an organ-support safety readout.

4.3 Relation to prior work

We extend the QRS-T angle literature (largest prior ICU study $n = 456$, manual measurement, static) [10–12] by two orders of magnitude in sample, add full adjustment and dose-response, and supply the missing longitudinal and event-prediction layers, building on the population evidence base [6–9]. Our null QTc result aligns with the inconsistency of the ICU QT literature [1–3] and offers an explanation: duration without spatial context is a weak descriptor of heterogeneity. The first-ECG sufficiency result explains the success of static deep-learning scores [13, 14] and bounds their achievable gain from longitudinal input for mortality (while our arrhythmia results show where longitudinal input does pay).

4.4 Strengths and limitations

Strengths: scale; a validated waveform engine with quantified error rates; prespecified landmark discipline eliminating immortal-time bias; ECG-specific outcomes analyzed under competing risks; and a positive-control-validated pharmacodynamic framework. Limitations: single center; machine-axis frontal-plane angle rather than true vectorcardiographic spatial angle; troponin surveillance was clinician-driven and sparse (myocardial-injury analyses are hypothesis-generating, and ascertainment bias is possible); arrhythmia outcomes rely on machine interpretation text; and all associations remain observational.

5. Conclusions

In critically ill patients without known heart disease, the spatial QRS-T angle is a strong, dose-graded, first-ECG prognostic marker; new-onset ST depression and QRS-T widening are early-warning signals for arrhythmia and myocardial injury; and the whole-cycle panel reads out intervention effects in vivo. QTc, the incumbent parameter, was uniformly uninformative. Whole-cycle ECG quantification — reproducible, automatable, and essentially free — deserves a place in ICU monitoring and in the endpoint definitions of critical-care trials.

Declarations

Ethical Approval and Consent to participate

The study protocol was approved by the Institutional Ethics Committee of Shanghai Pudong New Area People's Hospital (approval No. 2026-K82), which waived the requirement for individual informed consent. The MIMIC-IV (v3.1) and MIMIC-IV-ECG databases are publicly available, de-identified resources accessed under the PhysioNet Credentialed Data Use Agreement after completion of the required training.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed in this study (MIMIC-IV v3.1 and MIMIC-IV-ECG) are publicly available through PhysioNet under credentialed access. Cohort builders, panel builders (v1/v2), waveform engine v2, and all analysis scripts, with single-source results JSONs, are available from the corresponding author on reasonable request and will be deposited in a public repository with a permanent DOI before publication.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.H. (Hao) conceived the study, curated data, performed analysis, and drafted the manuscript. H.Y. performed analysis and drafted the manuscript. Q.Z., S.C., P.L., and J.W. interpreted results and revised the manuscript. All authors approved the final version.

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Tables

Tables 1 to 4 are available in the supplementary files section

Figures

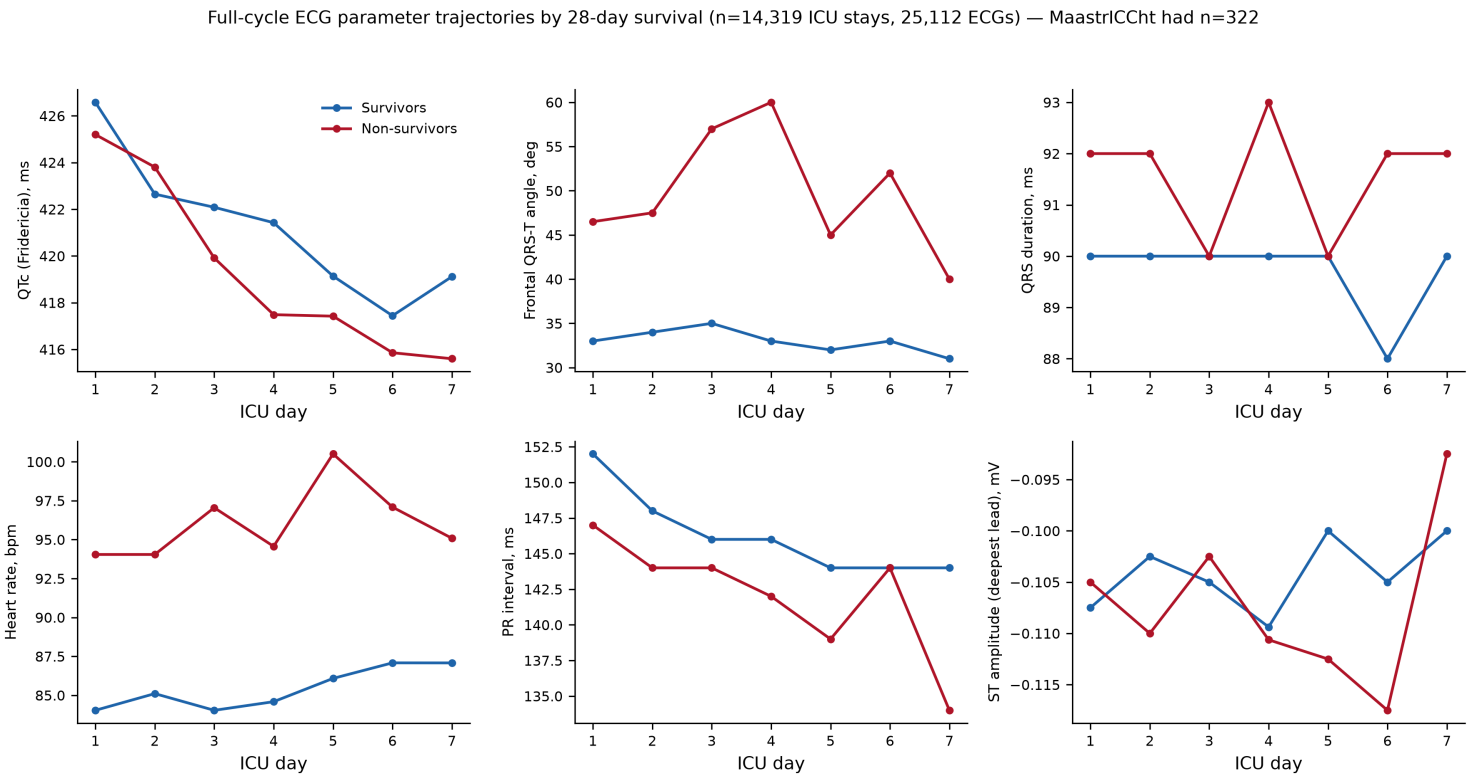


Figure 1

Whole-cycle trajectories by 28-day survival (fig1_efcd_trajectories.png)

EFCD flagship: full-cycle ECG dynamics in 14,319 ICU stays (MIMIC-IV-ECG)

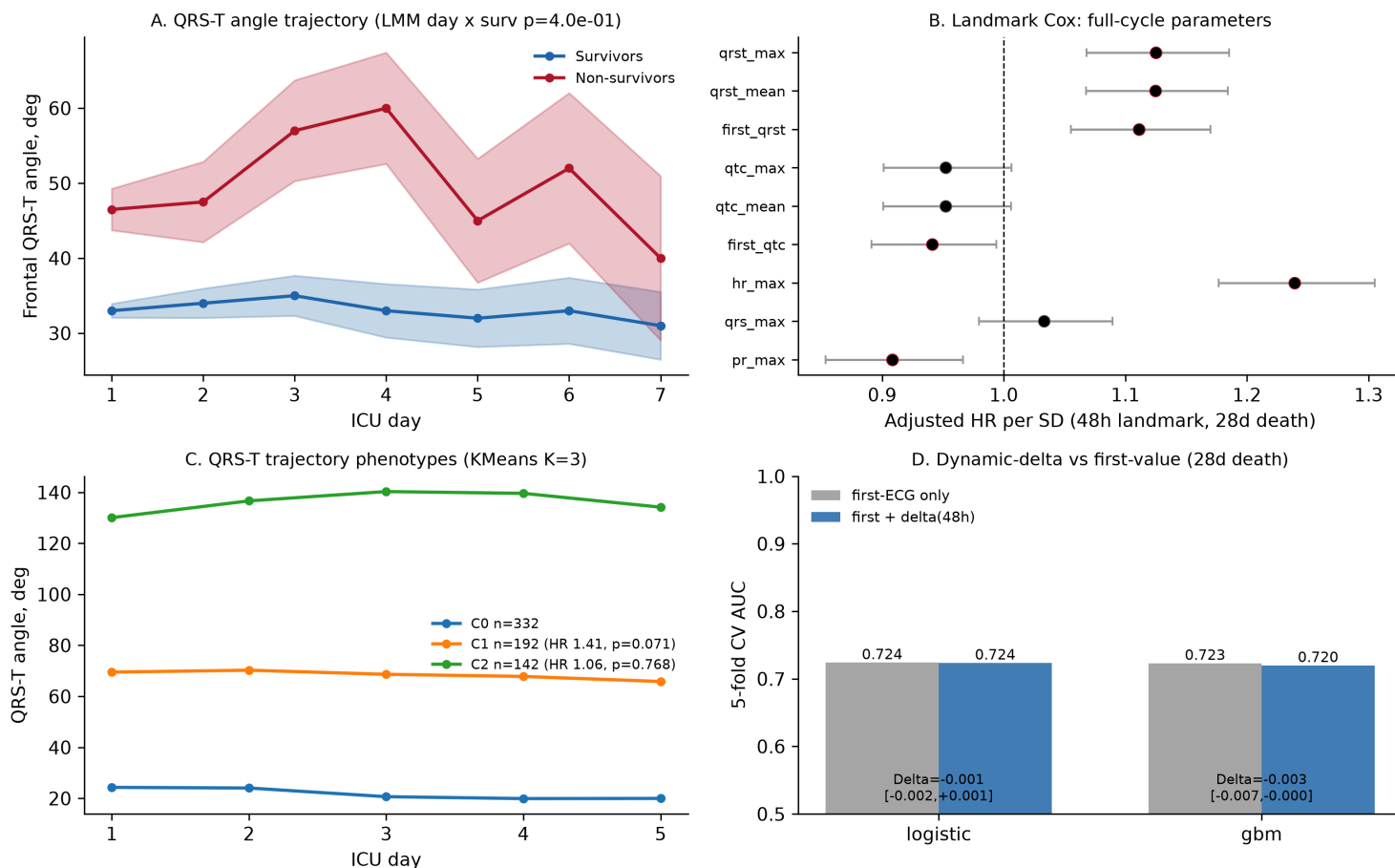


Figure 2

Flagship results: mixed-model trajectories, landmark forest, trajectory phenotypes, Δ -increment (fig2_efcd_flagship.png)

EFCD panel v2: corrected median-beat anchoring (n=11,382 landmark stays)

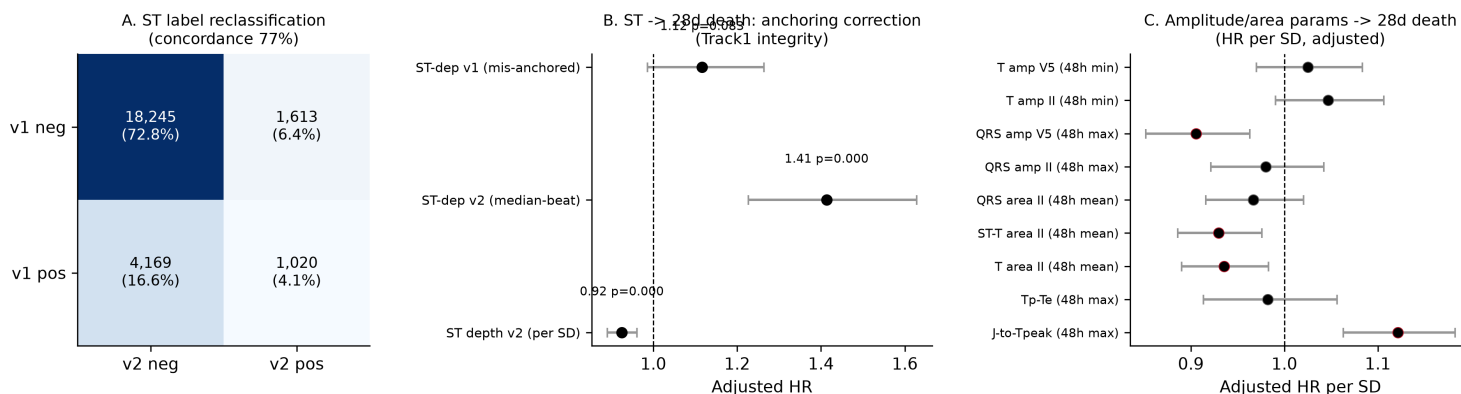


Figure 3

Waveform engine v2: corrected ST and amplitude parameters (fig3_efcd_v2_params.png)

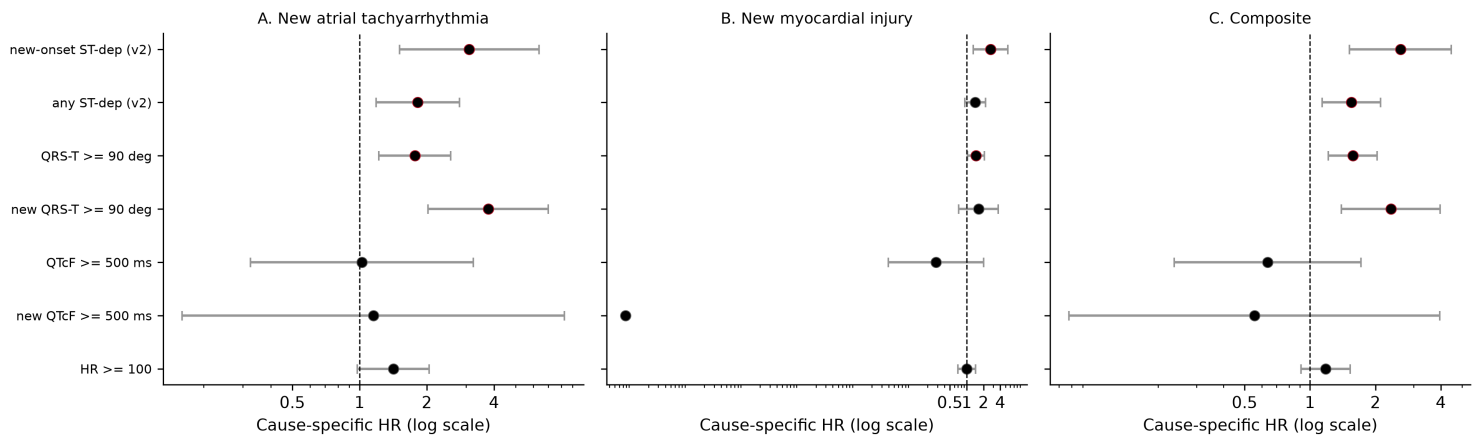


Figure 4

ECG-specific outcomes forest plots (fig4_efcd_cardiac.png)

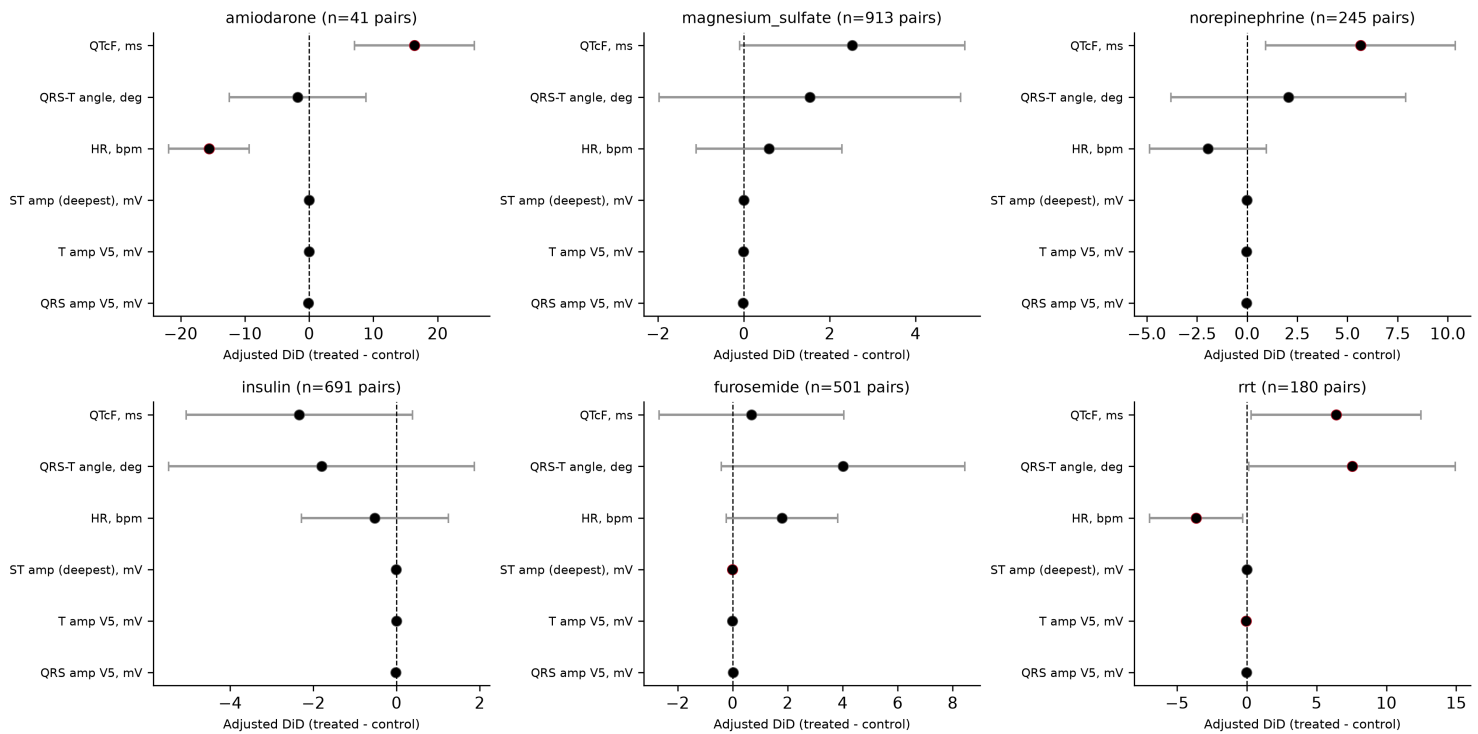


Figure 5

Pharmacodynamic difference-in-differences (fig5_efcd_pharmaco.png)

Supplementary Files

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