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Inadequate Heparin Responsiveness Before Cardiopulmonary Bypass: Definition-Dependent Frequency and Limited Discrimination by Routine Preoperative Laboratory Values

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Abstract

Background and Objectives: Weight-based heparin dosing before cardiopulmonary bypass (CPB) does not always achieve the target activated clotting time (ACT), and reported rates depend on the dose and threshold used. We aimed to identify routine preoperative laboratory values associated with an inadequate initial ACT response and to describe its definition-dependent frequency. *Materials and Methods:* At a tertiary center in Türkiye, this retrospective available-record cohort cross-referenced routine perfusion records with hospital information-system data at the person level for 638 adults undergoing cardiac surgery with CPB in 2023–2024 under a 300 IU/kg initial heparin protocol; this non-consecutive cohort represented 30.0% (638/2127) of CPB operations. The primary outcome was an arterial-blood ACT below 450 s measured 3 min after central venous administration of the initial dose; four alternative definitions were compared. *Results:* The primary outcome occurred in 176 patients (27.6%; 95% CI, 24.3–31.2%), and the proportion ranged from 14.1% (ACT below 400 s) to 43.6% (ACT below 480 s) across the five definitions. The prespecified 12-variable model was not statistically significant as a whole (likelihood-ratio $p = 0.135$), had poor discrimination (optimism-corrected area under the curve (AUC), 0.550), and identified no reliable routine predictor. Within this non-significant model, the C-reactive protein coefficient was nominally significant (adjusted odds ratio per 5 mg/L, 1.06; 95% CI, 1.01–1.12) and is hypothesis-generating only. The neutrophil-to-lymphocyte, platelet-to-lymphocyte, and systemic immune-inflammation indices did not discriminate (AUC, 0.510–0.531). In post hoc exploratory analyses, the 12-variable model for an ACT below 400 s was statistically significant ($p = 0.034$) but discriminated poorly (optimism-corrected AUC, 0.596), and weighting the cohort to all CPB operations by calendar quarter and type of surgery gave a similar frequency of the primary outcome (27.9%; 95% CI, 23.9–31.8%). *Conclusions:* An arterial-blood ACT below 450 s 3 min after central venous administration of 300 IU/kg was common in this available-record cohort, and its frequency varied more than threefold with the definition used. No routine preoperative variable evaluated, including C-reactive protein and the blood count-derived indices, was a reliable predictor or provided clinically useful discrimination before surgery.

Keywords: heparin responsiveness; heparin resistance; cardiopulmonary bypass; activated clotting time; C-reactive protein; cardiac surgery

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1. Introduction

Unfractionated heparin is the standard anticoagulant for cardiopulmonary bypass (CPB), and its effect is usually monitored with the activated clotting time (ACT) [1–4]. In some patients, a weight-based dose does not bring the ACT to the institutional target. This reduced responsiveness is commonly called heparin resistance. Definitions differ in the heparin dose, in the ACT threshold, and in whether redosing counts [1,2].

How often heparin resistance occurs depends on how it is defined. Reported incidence in adult cardiac surgery ranges from about 4% to more than 30%, because studies differ in heparin dose and ACT threshold [5,6]. A subcommittee of the International Society on Thrombosis and Haemostasis has proposed a standard definition: failure to reach an ACT of 480 s after 500 IU/kg [5]. It has not been adopted everywhere, and many centers use lower initial doses and targets [7]. Our institutional protocol uses 300 IU/kg and requires an ACT of at least 450 s before CPB.

Preoperative heparin therapy [8–11], a high platelet count [9,11], high fibrinogen [12,13], low albumin [11,13,14], and active infection or infective endocarditis [14,15] have each been reported as risk factors. These associations have not been consistent across cohorts. Kim et al. studied 605 patients and found no association between antithrombin activity and heparin resistance [15], and Ranucci et al. described resistance in patients whose antithrombin activity was normal [16]. Proposed explanations include binding of heparin to plasma proteins that rise during inflammation and neutralization by platelet factor 4 [17,18].

Several of these factors are linked to inflammation. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) come from the routine blood count at no additional cost. Gibson et al. related NLR to outcome after coronary artery bypass grafting [19]; SII was first described as a prognostic index after resection of hepatocellular carcinoma [20]. Evidence regarding these indices and heparin responsiveness during CPB is limited.

Our primary aim was to identify routine preoperative laboratory values associated with an inadequate arterial-blood ACT response 3 min after central venous administration of the institutional protocol-mandated 300 IU/kg dose of heparin in adults undergoing cardiac surgery with CPB. We also described the observed frequency under alternative ACT- and management-based definitions, tested whether NLR, PLR, and SII discriminated patients with an inadequate response, and compared perfusion characteristics and postoperative outcomes between ACT-response groups.

2. Materials and Methods

2.1. Study Design and Setting

This single-center retrospective available-record cohort study was conducted at the Department of Anesthesiology and Reanimation, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, a tertiary referral center. The study was approved by the institutional Medical Sciences Ethics Committee (decision no. 2024-TBEK 2026/08-21, 19 August 2026) and conducted in accordance with the Declaration of Helsinki. Informed consent was not obtained because this retrospective study used existing coded records without direct patient contact; the ethics committee approved the study protocol, which did not include an informed consent form. The analytic data were de-identified (coded): each patient was assigned a study code, and no direct identifiers were entered into the analytic data set. The report follows the STROBE statement [21].

2.2. Participants

Records of adult patients (aged 18 years or older) who underwent cardiac surgery with CPB from January 2023 onward were abstracted from the standard CPB record binders

kept by the perfusion unit and cross-referenced with the hospital information system. The approved protocol specified consecutive inclusion of eligible patients operated on between January 2023 and July 2026, with a minimum required sample size of 600 patients. Data abstraction began after ethics approval (19 August 2026) with the archived perfusion binders from 2023 and 2024, which were processed in folder batches rather than in chronological order. Once the minimum sample size had been exceeded, screening was pragmatically closed and the database was locked before any outcome analysis was performed. Consequently, records from 2025 and 2026 were not screened. This represented a deviation from the protocol-specified consecutive and longer inclusion plan. According to the hospital statistics module (queried on 19 October 2026), 2127 cardiac operations with CPB were performed in 2023–2024 (1058 in 2023 and 1069 in 2024), identified by procedure codes for on-pump coronary, valve, aortic, and other open-heart operations; off-pump coronary operations were not counted, and repeat CPB during the same admission was counted once. The last included operation took place on 30 December 2024. The resulting cohort was therefore a non-consecutive available-record sample of the CPB operations performed during the study period.

Inclusion required heparinization under the institutional protocol (300 IU/kg), recorded baseline and post-heparin ACT, and preoperative laboratory results in the hospital information system. We excluded off-pump operations, emergency or salvage procedures in which the standard heparinization protocol could not be followed, and repeat CPB during the same admission (only the first procedure was analyzed). Emergency operations in which the standard protocol was followed were retained. Records with missing or illegible ACT values, or with more than 20% of preoperative laboratory values missing, were also excluded. So were patients who had received antithrombin concentrate, fresh frozen plasma, or a direct thrombin inhibitor before surgery, those with known hereditary antithrombin deficiency or a history of heparin-induced thrombocytopenia, and those on preoperative extracorporeal membrane oxygenation or mechanical circulatory support.

Data abstraction generated 650 entries; these did not represent 650 distinct patients or operations. During data cleaning, 12 duplicate abstraction entries referring to the same patient and index operation were identified using the patient/protocol identifier and operation date. One copy of each duplicated entry was retained, leaving 638 unique patient-operation records for analysis; each included patient contributed one index operation. These records represent 30.0% of the 2127 CPB operations performed during the study period (quarterly range, 14.3–57.0%; Figure 1, Supplementary Table S1). The remaining 1489 operations were not individually screened because data abstraction was pragmatically closed after the minimum sample size had been exceeded; therefore, no operation-level eligibility assessment was performed and no exclusion reason was recorded.

2.3. Anticoagulation Protocol

ACT was measured with the Actalyke® MINI II coagulation analyzer (Helena Laboratories, Beaumont, TX, USA) using MAX-ACT reagent tubes, according to the manufacturer's instructions. Baseline ACT was measured before heparin administration. The institutional anticoagulation protocol mandated an initial intravenous dose of 300 IU/kg unfractionated heparin (heparin sodium 5000 IU/mL; Koparin 25,000 IU/5 mL vial, Koçak Farma, İstanbul, Türkiye) for all included patients; the dose was administered through central venous access. The post-heparin ACT was measured in arterial whole blood 3 min after administration. The time to reach the target ACT after redosing was not recorded on the paper perfusion forms. An ACT of at least 400 s was required for cannulation and at least 450 s for initiation of CPB. If the ACT was below target, approximately one-third of the initial dose was given and the ACT was repeated. During CPB, institutional practice, which was not specified

in the written protocol, was to keep the ACT at or above 400 s, with additional heparin given as needed. Additional doses and subsequent ACT measurements were recorded during the peri-CPB course, but the records did not show whether each additional dose was given before or after CPB initiation. After CPB, heparin was neutralized with protamine (Promin; Vem İlaç Sanayi, Tekirdağ, Türkiye). Intraoperative fresh frozen plasma was given routinely after protamine administration for hemostasis; the timing of individual units was not otherwise recorded on the perfusion form. The post-heparin ACT used for the primary outcome was measured before CPB initiation.

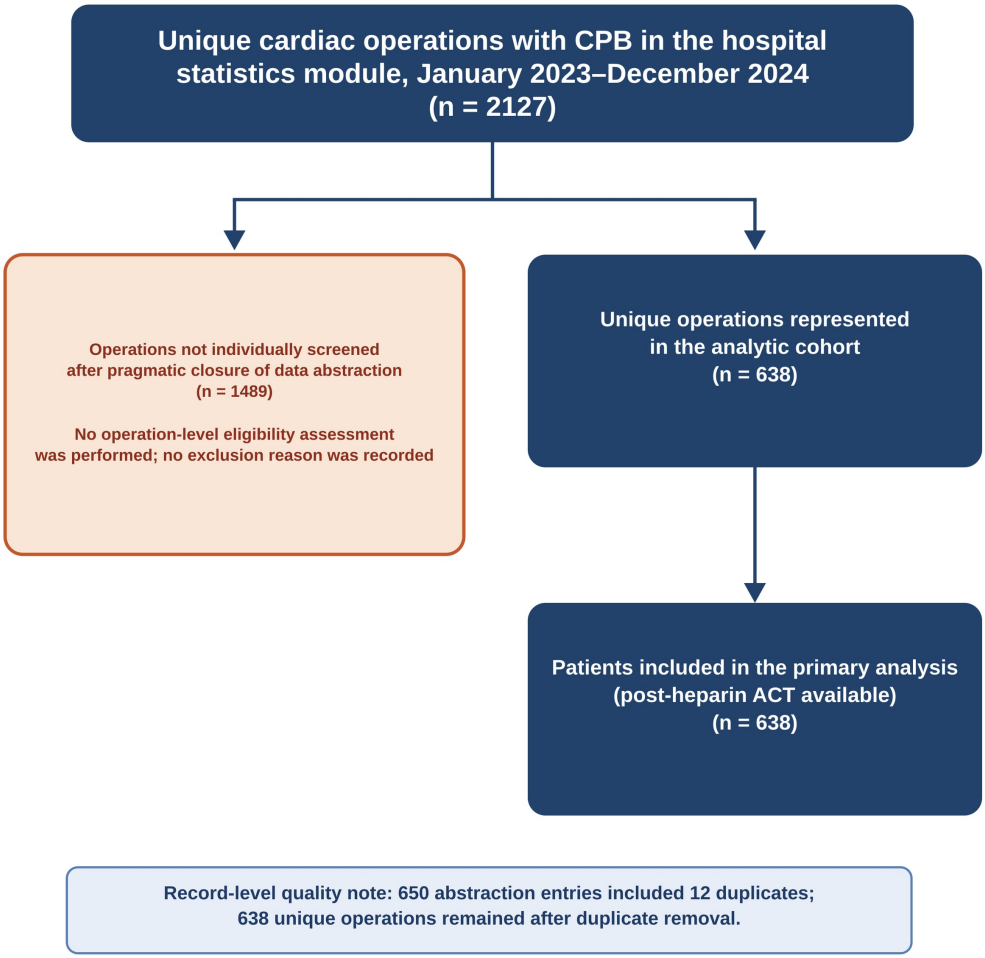

Figure 1. Assembly of the study cohort from all cardiac operations with CPB performed during the study period. The statistics module identified 2127 unique CPB operations. Of these, 638 unique patient-operation records were represented in the analytic cohort. The remaining 1489 operations were not individually screened because data abstraction was pragmatically closed after the minimum sample size had been exceeded; therefore, no operation-level eligibility assessment was performed and no exclusion reason was recorded. Record abstraction generated 650 entries; 12 duplicate abstraction entries referring to the same patient and index operation were removed, yielding 638 unique patient-operation records, with one index operation per patient.

For this study, the initial dose in international units was reconstructed by multiplying the recorded body weight by 300 IU/kg rather than abstracted as a separate administration variable. The perfusion form includes a field for the initial heparin dose, and at our center this dose is prepared from the 5000 IU/mL solution according to body weight. During screening, the recorded initial dose was checked against the protocol. One record (ÇK-364; 58 kg and 17,500 IU) corresponded to 301.7 IU/kg and was retained as a minor dosing-

rounding difference; no patient was excluded for this reason. Additional doses were obtained from the perfusion record. Total heparin dose was defined as the sum of the protocol-mandated initial dose and the recorded additional doses.

2.4. Definitions

The primary outcome was inadequate initial heparin responsiveness, defined as an arterial-blood ACT below 450 s measured 3 min after central venous administration of the 300 IU/kg protocol dose. Thirty-six patients (5.6%) had a post-heparin ACT of exactly 450 s confirmed on the perfusion record (35 without additional heparin and 1 with additional heparin) and were included in the comparison group (ACT $\geq$ 450 s); classifying ACT $\leq$ 450 s as an inadequate response was also evaluated in a post hoc exploratory sensitivity analysis. The study case-report form had defined heparin resistance as an ACT below 450 s after the 300 IU/kg protocol dose plus a requirement for additional heparin. Because the timing of additional doses was not recorded, we revised the primary definition to the initial ACT response alone. This revision was made after data abstraction, when the missing timing became apparent, and before any outcome frequencies or model results were examined; the two definitions differed by one patient (176 vs. 175). The original case-report-form definition is reported separately and is not included among the four alternative definitions. We evaluated four alternative definitions to show the effect of definition choice: a post-heparin ACT below 400 s; any additional heparin recorded during the peri-CPB course; a total recorded heparin dose of at least 400 IU/kg; and a post-heparin ACT below 480 s regardless of additional dosing. The first three were specified in the study protocol as sensitivity definitions; the last was added after protocol approval but before any analysis, because 480 s is the ACT target most often reported in the literature [5]. We treated definitions that included additional heparin as management-based and exploratory. In an additional post hoc exploratory sensitivity analysis, we evaluated a baseline-adjusted heparin sensitivity index (HSI = HSI = (post-heparin ACT − baseline ACT)/300 IU/kg < 1.0 s/(IU/kg), corresponding to an ACT increase < 300 s).

2.5. Variables and Data Sources

The following were taken from the perfusion record: age, sex, height, weight, body surface area, type of surgery, ACT values, additional heparin doses, CPB and aortic cross-clamp times, perfusion pressure, lowest temperature, lowest hemoglobin and hematocrit, peak lactate, priming volume, pump type, hemofiltration, intraoperative transfusion, and urine output. Body surface area was taken as recorded on the perfusion form and cross-checked against the DuBois formula (0.007184 × weight^0.425 × height^0.725); no record differed by more than 0.10 m^2. Sex was recorded as documented in the perfusion record; gender identity was not available in the retrospective data set.

Comorbidities, preoperative exposure to unfractionated or low-molecular-weight heparin, and oral anticoagulant and antiplatelet use were taken from the hospital information system. Preoperative laboratory values were the measurements closest to surgery within the preceding 7 days: hemoglobin, leukocyte, neutrophil, lymphocyte and platelet counts, C-reactive protein (CRP), albumin, creatinine, international normalized ratio, activated partial thromboplastin time, and fibrinogen. Estimated glomerular filtration rate was calculated with the 2021 CKD-EPI creatinine equation [22].

NLR, PLR, and SII (platelets × neutrophils/lymphocytes) were calculated from the blood count [20]. Antithrombin activity is not measured routinely at our center and was not available.

Postoperative outcomes were chest tube drainage in the first 24 h, transfusion, re-exploration for bleeding, duration of mechanical ventilation, acute kidney injury or renal

replacement therapy, cardiac, pulmonary, cerebrovascular, thromboembolic and infectious complications, lengths of intensive care unit and total hospital stay (defined from index hospital admission to discharge, including the preoperative inpatient diagnostic and surgical preparation period), and recorded 30-day mortality. Postoperative complications were abstracted as recorded on the study case-report form. Thirty-day mortality was available as a binary field on that form; the underlying ascertainment pathway and completeness of post-discharge follow-up were not separately documented. The form grouped myocardial infarction and arrhythmia as cardiac complications, listed pneumonia under pulmonary complications, combined infection with sepsis, and recorded acute kidney injury together with renal replacement therapy. It did not specify separate diagnostic criteria for these events. Prolonged ventilation was defined as more than 24 h.

2.6. Data Quality

Before database lock, all 638 records underwent automated consistency and plausibility checks (absolute difference between recorded and DuBois body surface area ≤ 0.10 m^2; preoperative and intraoperative hematocrit-to-hemoglobin ratio 2.5–3.5) together with source-verification flagging. This screen selected 322 records (50.5%), in which the 11-test preoperative laboratory block (hemoglobin; leukocyte, neutrophil, lymphocyte, and platelet counts; C-reactive protein; albumin; creatinine; international normalized ratio; activated partial thromboplastin time; and fibrinogen) was re-extracted from the hospital information system and corrected against the source. All re-extractions and corrections were completed before database lock and before analysis. Preoperative hematocrit was re-extracted in 1 additional record, and all 36 records with a post-heparin ACT of exactly 450 s were separately verified against the original paper perfusion charts. To check the screen, a second investigator independently compared the primary study variables with the source perfusion forms and hospital information system in 64 randomly selected records and 2 targeted quality-control records (66 records in total). The 38 random audit records that had not been selected by the screen, a random subsample of the 316 unselected records (12.0%), showed no discrepancies (0 of 38; 95% Wilson CI, 0.0–9.2%). The other 26 random audit records (40.6%) had laboratory-block transcription discrepancies in the original abstraction; all 26 were among the 322 records selected by the screen, and all discrepancies were corrected from the source hospital information system. Perfusion-chart variables were concordant in all 64 random audit records. Because the audit findings overlapped with the records selected for re-extraction, this comparison was descriptive and was not used to estimate screening sensitivity or a detection rate. Apart from antithrombin activity and time to reach the target ACT, which were not available, there were no missing values in any variable reported in Table 1, Supplementary Table S2, so no imputation was performed. Zero entries in later serial ACT fields were treated as unavailable measurements in the exploratory redosing analysis.

Table 1. Baseline characteristics and preoperative laboratory values.

Variable	All Patients (n = 638)	ACT < 450 s (n = 176)	ACT ≥ 450 s (n = 462)	p
Age, years	61 (57–66)	62 (56–67)	61 (57–66)	0.808
Male sex	516 (80.9)	133 (75.6)	383 (82.9)	0.035
Body mass index, kg/m^2	28.2 (26.0–31.2)	27.8 (25.8–31.8)	28.4 (26.0–31.2)	0.883
Body surface area, m^2	1.90 (1.81–2.00)	1.90 (1.78–2.01)	1.90 (1.82–2.00)	0.597

Table 1. *Cont.*

Variable	All Patients (n = 638)	ACT < 450 s (n = 176)	ACT ≥ 450 s (n = 462)	p
Type of surgery				0.643
Isolated CABG	439 (68.8)	115 (65.3)	324 (70.1)	
Valve	81 (12.7)	28 (15.9)	53 (11.5)	
CABG + valve	69 (10.8)	19 (10.8)	50 (10.8)	
Aortic	33 (5.2)	9 (5.1)	24 (5.2)	
Other	16 (2.5)	5 (2.8)	11 (2.4)	
Emergency surgery	34 (5.3)	10 (5.7)	24 (5.2)	0.807
Hypertension	467 (73.2)	134 (76.1)	333 (72.1)	0.301
Diabetes mellitus	262 (41.1)	75 (42.6)	187 (40.5)	0.624
Congestive heart failure	124 (19.4)	32 (18.2)	92 (19.9)	0.621
COPD/asthma	86 (13.5)	23 (13.1)	63 (13.6)	0.851
Chronic kidney disease	25 (3.9)	5 (2.8)	20 (4.3)	0.387
Atrial fibrillation	50 (7.8)	16 (9.1)	34 (7.4)	0.467
Cerebrovascular disease	39 (6.1)	10 (5.7)	29 (6.3)	0.779
Malignancy	23 (3.6)	5 (2.8)	18 (3.9)	0.523
Active infection	13 (2.0)	5 (2.8)	8 (1.7)	0.361
Preoperative heparin/LMWH exposure	551 (86.4)	154 (87.5)	397 (85.9)	0.606
Duration of exposure, days (exposed only)	9 (5–12)	9 (5–13)	8 (5–12)	0.704
Preoperative oral anticoagulant	38 (6.0)	5 (2.8)	33 (7.1)	0.040
Preoperative antiplatelet	418 (65.5)	116 (65.9)	302 (65.4)	0.898
Hemoglobin, g/dL	13.6 (12.4–14.8)	13.8 (12.5–14.9)	13.5 (12.3–14.7)	0.509
Leukocytes, $\times 10^3/\mu L$	8.36 (7.02–9.90)	8.46 (7.14–10.11)	8.35 (6.89–9.79)	0.480
Neutrophils, $\times 10^3/\mu L$	5.19 (4.29–6.43)	5.46 (4.49–6.46)	5.07 (4.25–6.40)	0.132
Lymphocytes, $\times 10^3/\mu L$	2.16 (1.67–2.74)	2.14 (1.71–2.73)	2.18 (1.66–2.75)	0.950
Platelets, $\times 10^3/\mu L$	253 (211–296)	254 (217–296)	252 (210–297)	0.618
NLR	2.42 (1.86–3.26)	2.49 (1.95–3.12)	2.38 (1.83–3.28)	0.260
PLR	117.6 (88.9–157.9)	117.1 (93.1–151.4)	118.3 (85.4–159.3)	0.686
SII	608 (445–824)	621 (465–836)	604 (435–816)	0.230
C-reactive protein, mg/L	8.9 (5.1–13.5)	9.5 (5.8–15.3)	8.6 (5.0–13.3)	0.025
Albumin, g/dL	4.07 (3.84–4.28)	4.08 (3.79–4.28)	4.07 (3.85–4.29)	0.701
Creatinine, mg/dL	0.92 (0.77–1.12)	0.95 (0.77–1.12)	0.91 (0.77–1.12)	0.593
eGFR, mL/min/1.73 m^2	88.5 (69.8–101.2)	86.5 (66.7–102.0)	89.5 (70.2–101.1)	0.470
INR	0.99 (0.93–1.06)	1.00 (0.93–1.07)	0.98 (0.93–1.06)	0.259
aPTT, s	23.4 (21.4–26.0)	23.6 (21.5–26.2)	23.4 (21.4–25.7)	0.567
Fibrinogen, mg/dL	350 (289–422)	353 (301–438)	349 (286–419)	0.355
Baseline ACT, s	152 (143–161)	151 (142–158)	152 (144–162)	0.087

Values are median (interquartile range) or n (%). Continuous variables were compared with the Mann–Whitney U test and categorical variables with the Pearson chi-square or Fisher exact test. ACT, activated clotting time; aPTT, activated partial thromboplastin time; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

2.7. Statistical Analysis

The sample size was based on the multivariable model. Using the conventional approximation of 10 outcome events per model parameter, the 12 prespecified candidate variables required at least 120 primary-outcome events (12 × 10) [23]. Assuming a 20% event frequency, this corresponded to a minimum total sample of 600 patients (120/0.20). The ACT-based primary outcome occurred in 176 patients, corresponding to 14.7 events per candidate variable (176/12). Each candidate variable was entered as a single continuous or binary term, so the 12 variables corresponded to 12 model parameters. The model was intended to estimate adjusted associations rather than to develop a clinical prediction model. Because the events-per-variable rule does not account for expected model fit or the need for shrinkage [24], model optimism and calibration were assessed directly by bootstrap internal validation.

Continuous variables are reported as median (interquartile range) and were compared with the Mann–Whitney U test. Categorical variables are reported as number (%) and were compared with the Pearson chi-square or Fisher exact test, as appropriate. Proportions are reported with Wilson 95% confidence intervals (CI). Group comparisons were descriptive and exploratory.

Variables for the multivariable logistic regression were selected before analysis from the protocol and previous reports: age, sex, body mass index, preoperative heparin exposure, hemoglobin, leukocyte count, platelet count, CRP, albumin, fibrinogen, estimated glomerular filtration rate, and baseline ACT. All 12 were entered simultaneously. CRP was prespecified as an untransformed continuous variable (scaled per 5 mg/L), and this model is presented as the primary multivariable analysis. Because the distribution of CRP was right-skewed, a log2 transformation of CRP (per doubling), restricted cubic splines (3 and 4 knots at standard percentiles), and truncation of CRP at its 99th percentile (84.0 mg/L) were examined in post hoc exploratory analyses and compared using likelihood-ratio tests and the Akaike information criterion (AIC) (Supplementary Table S3). Results are reported as adjusted odds ratios (aOR) with 95% CI. Collinearity was assessed with variance inflation factors, calibration with the Hosmer–Lemeshow test, and discrimination with the AUC. Internal validation used 1000 bootstrap resamples to estimate optimism-corrected AUC, Brier score, calibration slope, and calibration-in-the-large (intercept estimated with the slope fixed at 1).

The ability of NLR, PLR, SII, and CRP to discriminate patients with an inadequate initial ACT response was assessed with AUC and DeLong 95% CI [25]. Youden cut-offs were retained only as exploratory, data-derived estimates and were not interpreted as validated clinical thresholds.

The same 12-variable model was fitted under each alternative definition (both with untransformed CRP and post hoc log2-transformed CRP; Supplementary Tables S3 and S4) and under two post hoc exploratory outcome definitions (ACT $\leq$ 450 s and baseline-adjusted HSI $<$ 1.0 s/[IU/kg]). In a further post hoc exploratory check, the primary model was refitted after adding active infection, type of surgery (isolated coronary artery bypass grafting vs. other), urgency, and calendar year of surgery (2024 vs. 2023). Three further post hoc exploratory analyses were added during peer review. First, the frequency under each definition was re-estimated after weighting the cohort to the distribution of all 2127 CPB operations by calendar quarter and type of surgery (iterative proportional fitting to the marginal totals in Supplementary Table S1), with percentile 95% CI from 2000 bootstrap resamples; a second weighting added emergency status. Second, for the definition based on an ACT below 400 s, we report overall model fit, discrimination with bootstrap optimism correction, and the AUC of NLR, PLR, SII, and CRP. Third, baseline ACT and the HSI were

compared between patients with and without preoperative heparin exposure. None of the post hoc analyses was a prespecified endpoint, and all are reported as exploratory.

Comparisons of perfusion characteristics and postoperative outcomes were exploratory and were not adjusted for multiple testing. Two-sided p values below 0.05 were considered statistically significant. Statistical analyses were performed using Python 3.11 (Python Software Foundation, Wilmington, DE, USA) with NumPy 1.26, pandas 2.2, SciPy 1.12, statsmodels 0.14, and scikit-learn 1.4; the analysis code is available from the corresponding author on reasonable request. Analysis code was written with the assistance of Claude Opus 5.5 (Anthropic, San Francisco, CA, USA) and Codex (OpenAI, San Francisco, CA, USA; GPT-5.6 Sol) and was verified by the authors. The same tools were used to assist with drafting and English-language editing of the manuscript; all text was reviewed and revised by the authors.

3. Results

3.1. Study Population

The analysis included 638 patients, each represented by one index operation (Figure 1, Table 1). Median age was 61 years (interquartile range (IQR), 57–66), and 516 (80.9%) were men. Isolated coronary artery bypass grafting was the most common procedure (439 patients, 68.8%), followed by valve surgery (81, 12.7%), combined coronary and valve surgery (69, 10.8%), aortic surgery (33, 5.2%), and other procedures (16, 2.5%). Thirty-four operations (5.3%) were emergencies. Before surgery, 551 patients (86.4%) had received unfractionated or low-molecular-weight heparin, for a median of 9 days (IQR, 5–12).

3.2. Frequency of Inadequate Heparin Responsiveness

Median ACT after the initial dose was 499 s (IQR, 438–560) (Figure 2). The primary outcome, an arterial-blood ACT below 450 s measured 3 min after central venous heparin administration, occurred in 176 patients (27.6%; 95% CI, 24.3–31.2%). The rate was similar in 2023 (63 of 216, 29.2%) and 2024 (113 of 422, 26.8%; $p = 0.523$); across the eight calendar quarters from Q1 2023 to Q4 2024, quarterly case counts were 58, 49, 58, 51, 163, 107, 113, and 39, and quarterly proportions of ACT < 450 s ranged from 22.4% to 37.9%. The included patients represented 14.3% to 57.0% of the CPB operations performed in each quarter (Supplementary Table S1). In a post hoc exploratory analysis that weighted the cohort to the distribution of all 2127 CPB operations by calendar quarter and type of surgery, the proportion with the primary outcome was 27.9% (95% CI, 23.9–31.8%); it was 28.2% (95% CI, 24.0–32.2%) when emergency status was added to the weighting (Supplementary Table S5).

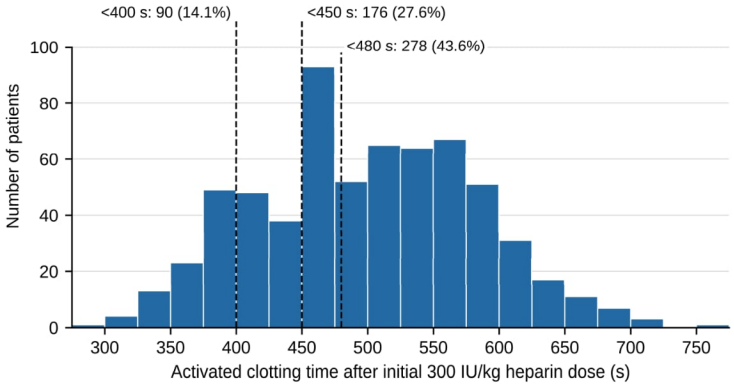

Figure 2. Distribution of arterial-blood activated clotting time 3 min after central venous administration of the 300 IU/kg protocol dose of heparin (n = 638). Dashed lines mark ACT thresholds of 400, 450, and 480 s; ACT < 450 s was the primary outcome.

Observed frequency varied more than threefold across definitions (Table 2). It was 14.1% for an ACT below 400 s (all of whom had recorded additional heparin), 23.2% for a total dose of at least 400 IU/kg (60 patients had a total of exactly 400 IU/kg), 27.6% for the primary outcome (33.2% (212 of 638; 95% CI, 29.7–37.0%) when the 36 patients with an ACT of exactly 450 s were included as ACT ≤ 450 s, and 32.6% (208 of 638; 95% CI, 29.1–36.3%) for baseline-adjusted HSI < 1.0 s/(IU/kg)), 33.9% for any recorded additional heparin, and 43.6% for an ACT below 480 s. The original case-report-form definition (ACT below 450 s with additional heparin) identified 175 patients (27.4%; 95% CI, 24.1–31.0%). Across the five definitions in Table 2, 341 patients (53.4%) met none, 88 (13.8%) met one, 22 (3.4%) met two, 38 (6.0%) met three, 83 (13.0%) met four, and 66 (10.3%) met all five.

Table 2. Frequency of inadequate heparin responsiveness under five definitions (n = 638).

Definition	*n*	%	95% CI
Primary: post-heparin ACT < 450 s	176	27.6	24.3–31.2
Post-heparin ACT < 400 s	90	14.1	11.6–17.0
Post-heparin ACT < 480 s	278	43.6	39.8–47.4
Any additional heparin recorded during the peri-CPB course	216	33.9	30.3–37.6
Total heparin ≥ 400 IU/kg	148	23.2	20.1–26.6

Wilson 95% confidence intervals. All 90 patients with a post-heparin ACT < 400 s also had recorded additional heparin. Protocol-derived initial dose of 300 IU/kg in all patients (not individually recorded); arterial-blood ACT measured 3 min after central venous administration of the initial dose.

All but one of the 176 patients with an ACT below 450 s had recorded additional heparin. Additional heparin was also recorded in 41 of the 462 patients (8.9%) whose ACT was 450 s or above (Supplementary Table S6). A later recorded ACT below 450 s was found in 24 of these 41 patients (58.5%) and in 197 of the 421 (46.8%) who received no additional heparin. In 153 of these 197 patients, the lowest later value was between 400 and 449 s, within the institutional maintenance target of at least 400 s during CPB; the other 44 had at least one later value below 400 s (lowest value: median, 362 s; range, 228–399) without recorded additional heparin. In 11 records, the perfusion notes mentioned fresh frozen plasma given during CPB alongside low or borderline serial ACT values. Patients meeting the primary outcome had a median post-heparin ACT of 399 s (IQR, 375–421) (Table 3).

Table 3. Anticoagulation and cardiopulmonary bypass characteristics by initial ACT response.

Variable	All Patients (*n* = 638)	ACT < 450 s (*n* = 176)	ACT ≥ 450 s (*n* = 462)	*p*
ACT after initial heparin, s	499 (438–560)	399 (375–421)	530 (487–576)	<0.001
Any additional heparin during the recorded peri-CPB course	216 (33.9)	175 (99.4)	41 (8.9)	<0.001
Additional heparin, IU/kg	0 (0–79)	100 (86–200)	0 (0–0)	<0.001
Total heparin dose, IU/kg	300 (300–379)	400 (386–500)	300 (300–300)	<0.001
CPB duration, min	107 (91–135)	106 (91–134)	108 (91–135)	0.734
Aortic cross-clamp time, min	75 (63–95)	78 (64–97)	75 (63–95)	0.552
Mean perfusion pressure, mmHg	68 (66–74)	68 (65–73)	69 (67–74)	0.071
Minimum perfusion pressure, mmHg	55 (53–60)	57 (52–60)	55 (54–60)	0.921
Lowest temperature, °C	31.4 (29.9–33.2)	31.4 (30.0–33.0)	31.5 (29.7–33.2)	0.768
Lowest hematocrit on CPB, %	24.4 (22.0–27.1)	24.6 (22.0–27.4)	24.4 (21.9–27.0)	0.639

Table 3. *Cont.*

Variable	All Patients (n = 638)	ACT < 450 s (n = 176)	ACT ≥ 450 s (n = 462)	p
Lowest hemoglobin on CPB, g/dL	8.1 (7.2–8.9)	8.1 (7.3–8.9)	8.1 (7.1–8.8)	0.804
Peak lactate on CPB, mmol/L	2.45 (2.04–3.08)	2.51 (2.01–3.15)	2.42 (2.04–3.04)	0.526
Hemofiltration	51 (8.0)	17 (9.7)	34 (7.4)	0.338
Centrifugal pump	93 (14.6)	19 (10.8)	74 (16.0)	0.095
Priming volume, mL	1200 (1000–1400)	1150 (988–1400)	1250 (1000–1400)	0.202
Urine output, mL	900 (700–1400)	900 (600–1412)	900 (700–1400)	0.409
Intraoperative RBC, units	0 (0–2)	0 (0–2)	0 (0–2)	0.192
Intraoperative FFP, units	2 (0–3)	2 (0–3)	2 (0–3)	0.267
Any intraoperative RBC	233 (36.5)	69 (39.2)	164 (35.5)	0.385
Any intraoperative FFP	390 (61.1)	106 (60.2)	284 (61.5)	0.773

Values are median (interquartile range) or n (%). Additional heparin indicates any dose recorded during the peri-CPB course; timing relative to CPB initiation was unavailable. CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; RBC, red blood cell concentrate.

3.3. Preoperative Characteristics

Baseline characteristics are shown in Table 1. Patients with an inadequate initial ACT response were less often men (75.6% vs. 82.9%; $p = 0.035$), were less often receiving oral anticoagulants (2.8% vs. 7.1%; $p = 0.040$), and had higher CRP (median, 9.5 mg/L (IQR, 5.8–15.3) vs. 8.6 mg/L (IQR, 5.0–13.3); $p = 0.025$). Baseline ACT did not differ between patients with and without preoperative oral anticoagulant exposure (median, 152 s (IQR, 144–162) vs. 152 s (IQR, 143–161); $p = 0.726$). The groups did not differ in age, body mass index, type or urgency of surgery, or comorbidities.

Preoperative heparin exposure was similar between the groups (87.5% vs. 85.9%; $p = 0.606$), as was its duration. In a post hoc exploratory comparison, baseline ACT did not differ between patients with and without preoperative heparin exposure (median, 152 s (IQR, 143–161) vs. 151 s (IQR, 143–163); $p = 0.941$), nor did the HSI (median, 1.15 vs. 1.14 s/[IU/kg]; $p = 0.677$). Among exposed patients, baseline ACT was not correlated with the duration of exposure (Spearman $\rho = -0.01$; $p = 0.807$). Hemoglobin, leukocyte, neutrophil, lymphocyte and platelet counts, albumin, creatinine, eGFR, fibrinogen, coagulation tests, and baseline ACT showed no significant difference. NLR, PLR, and SII were also similar ($p = 0.260$, 0.686, and 0.230, respectively).

3.4. Multivariable Analysis

In the prespecified primary model with untransformed CRP, the model as a whole was not statistically significant (likelihood-ratio $p = 0.135$; AIC, 760.2) and identified no reliable routine predictor of an inadequate initial ACT response (Table 4, Figure 3). Within this non-significant model, the CRP coefficient was nominally significant (aOR per 5 mg/L, 1.06; 95% CI, 1.01–1.12; $p = 0.027$); we interpret this isolated coefficient as hypothesis-generating only. Baseline ACT (aOR per 10 s, 0.89; 95% CI, 0.79–1.01; $p = 0.067$) and male sex (aOR, 0.65; 95% CI, 0.42–1.02; $p = 0.062$) were not significantly associated after adjustment, nor were preoperative heparin exposure, hemoglobin, leukocyte count, platelet count, albumin, fibrinogen, or eGFR. In the post hoc exploratory model with log2-transformed CRP (Supplementary Table S3), CRP (aOR per doubling, 1.25; 95% CI, 1.06–1.46; $p = 0.007$) and baseline ACT (aOR per 10 s, 0.88; 95% CI, 0.78–1.00; $p = 0.046$) showed similar estimates, while the overall model remained borderline (likelihood-ratio $p = 0.072$; AIC, 757.8).

Table 4. Univariable and multivariable logistic regression for the primary ACT-based outcome (prespecified primary model with untransformed C-reactive protein).

Variable	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age (per 10 years)	1.04 (0.86–1.25)	0.717	1.02 (0.83–1.25)	0.847
Male sex	0.64 (0.42–0.97)	0.036	0.65 (0.42–1.02)	0.062
BMI (per 1 kg/m^2)	1.01 (0.97–1.05)	0.589	1.01 (0.97–1.05)	0.716
Preoperative heparin/LMWH exposure	1.15 (0.68–1.92)	0.606	1.25 (0.73–2.13)	0.419
Hemoglobin (per 1 g/dL)	1.01 (0.92–1.11)	0.797	1.05 (0.94–1.17)	0.360
Leukocytes (per 1 ×10^3/μL)	1.02 (0.95–1.10)	0.527	1.00 (0.92–1.08)	0.987
Platelets (per 50 ×10^3/μL)	1.05 (0.92–1.20)	0.482	1.06 (0.93–1.22)	0.380
C-reactive protein (per 5 mg/L)	1.06 (1.01–1.11)	0.024	1.06 (1.01–1.12)	0.027
Albumin (per 1 g/dL)	0.85 (0.52–1.39)	0.511	0.98 (0.56–1.72)	0.940
Fibrinogen (per 50 mg/dL)	1.06 (0.97–1.17)	0.176	1.07 (0.97–1.17)	0.174
eGFR (per 10 mL/min/1.73 m^2)	0.95 (0.88–1.03)	0.222	0.98 (0.89–1.07)	0.597
Baseline ACT (per 10 s)	0.89 (0.78–1.00)	0.054	0.89 (0.79–1.01)	0.067

n = 638; 176 events (14.7 events per variable). All 12 variables were entered simultaneously in the prespecified primary model with untransformed C-reactive protein (per 5 mg/L). Overall model likelihood-ratio $p = 0.135$; Nagelkerke $R^2 = 0.039$; Hosmer–Lemeshow $\chi^2 = 3.47$, df = 8, $p = 0.902$; apparent AUC = 0.604 (95% CI, 0.555–0.653); bootstrap optimism-corrected AUC = 0.550; highest variance inflation factor = 1.28. In the post hoc exploratory model with log2-transformed C-reactive protein (Supplementary Table S3), the unadjusted OR per doubling of C-reactive protein was 1.23 (95% CI, 1.06–1.42; $p = 0.007$), the adjusted OR was 1.25 (95% CI, 1.06–1.46; $p = 0.007$), and the overall likelihood-ratio p was 0.072 (apparent AUC = 0.606; optimism-corrected AUC = 0.555). BMI, body mass index; OR, odds ratio.

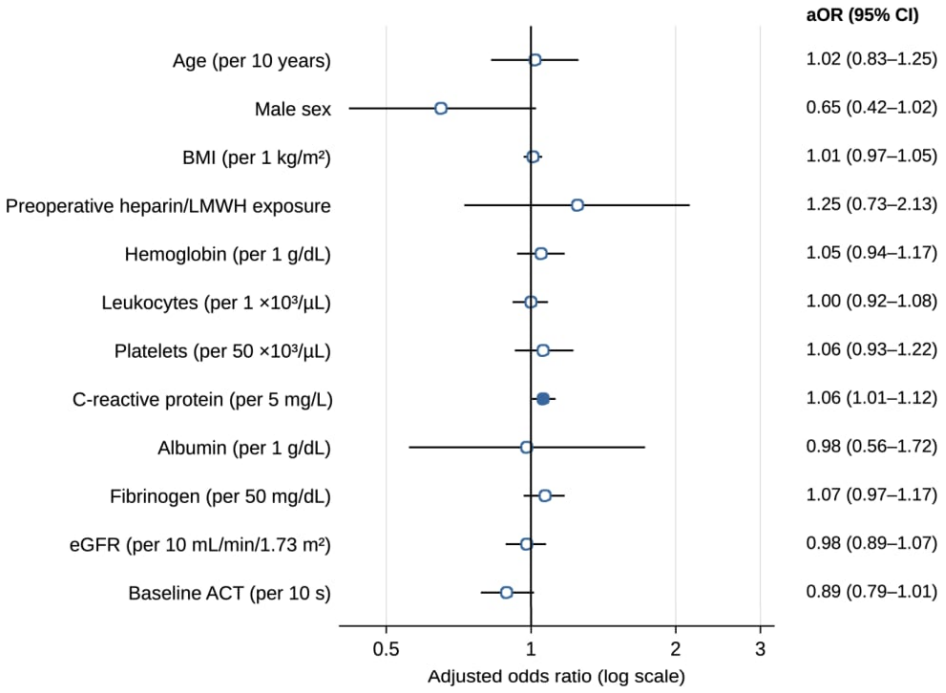

Figure 3. Adjusted odds ratios with 95% confidence intervals for the primary outcome (arterial-blood ACT < 450 s measured 3 min after central venous heparin administration) from the prespecified 12-variable multivariable logistic regression model with untransformed C-reactive protein (per 5 mg/L). The horizontal axis is logarithmic. Filled circle indicates a nominal $p < 0.05$ for an individual coefficient (C-reactive protein, $p = 0.027$); the overall model was not statistically significant (likelihood-ratio $p = 0.135$).

The prespecified linear model explained little of the variation (Nagelkerke R^2, 0.039) and had poor apparent discrimination (AUC, 0.604; 95% CI, 0.555–0.653). The Hosmer–Lemeshow test did not indicate lack of fit ($\chi^2 = 3.47$, df = 8, $p = 0.902$), and the highest variance inflation factor was 1.28. After 1000 bootstrap resamples, the optimism-corrected AUC was 0.550, the corrected Brier score was 0.203, the calibration slope was 0.584, and calibration-in-the-large was 0.00 (in the post hoc exploratory log2 model, apparent AUC was 0.606, optimism-corrected AUC was 0.555, corrected Brier score was 0.202, and calibration slope was 0.626).

3.5. Inflammatory Indices

None of the blood count-derived indices discriminated patients with an inadequate initial ACT response (Table 5). The AUC was 0.529 (95% CI, 0.481–0.577) for NLR, 0.510 (95% CI, 0.461–0.559) for PLR, and 0.531 (95% CI, 0.482–0.580) for SII. CRP performed slightly better than chance (AUC, 0.557; 95% CI, 0.507–0.608; $p = 0.025$). The data-derived Youden cut-offs are reported as exploratory estimates only.

Table 5. Discrimination of preoperative inflammatory markers for the primary ACT-based outcome.

Marker	AUC (95% CI)	*p*	Exploratory Youden Cut-Off	Sensitivity, %	Specificity, %
NLR	0.529 (0.481–0.577)	0.241	≥2.10	69.9	41.3
PLR	0.510 (0.461–0.559)	0.679	≥89.11	80.1	27.3
SII	0.531 (0.482–0.580)	0.217	≥378.30	90.3	18.0
C-reactive protein	0.557 (0.507–0.608)	0.025	≥5.44	80.1	31.0

Confidence intervals by the DeLong method; *p* for the null hypothesis AUC = 0.5. Cut-offs are reported for completeness; with AUC values close to 0.5, they have no clinical use.

3.6. Sensitivity Analyses

Under the alternative definitions, the association with CRP remained in the same direction across all specifications (Supplementary Tables S3 and S4). In the prespecified linear model, CRP (per 5 mg/L) was associated with any recorded additional heparin (aOR, 1.06; 95% CI, 1.00–1.11; $p = 0.037$) and an ACT below 480 s (aOR, 1.06; 95% CI, 1.01–1.12; $p = 0.022$), but not with an ACT below 400 s (aOR, 1.02; 95% CI, 0.95–1.09; $p = 0.643$) or a total dose of at least 400 IU/kg (aOR, 1.06; 95% CI, 1.00–1.12; $p = 0.055$). In the post hoc exploratory log2-CRP models (Supplementary Table S3), the aOR per doubling of CRP was 1.22 (95% CI, 1.05–1.42; $p = 0.011$) for any additional heparin, 1.19 (95% CI, 1.03–1.37; $p = 0.021$) for an ACT below 480 s, 1.12 (95% CI, 0.91–1.37; $p = 0.295$) for an ACT below 400 s, and 1.21 (95% CI, 1.02–1.43; $p = 0.027$) for a total dose of at least 400 IU/kg. In a post hoc exploratory analysis in which the 36 patients with a post-heparin ACT of exactly 450 s were included in the outcome (ACT ≤ 450 s, 212 events [33.2%]), the aOR per 5 mg/L of CRP was 1.07 (95% CI, 1.01–1.12; $p = 0.015$; log2-CRP aOR per doubling, 1.30; 95% CI, 1.11–1.51; $p = 0.001$).

Several other associations appeared in individual sensitivity models (Supplementary Tables S3 and S4). At the 400 s threshold, which other centers use as the target before CPB [26], 90 patients (14.1%; 95% CI, 11.6–17.0%) had an inadequate response. In the same 12-variable model, CRP was not associated with this outcome (aOR per 5 mg/L, 1.02; 95% CI, 0.95–1.09; $p = 0.643$), whereas fibrinogen (aOR per 50 mg/dL, 1.21; 95% CI, 1.08–1.37; $p = 0.002$) and baseline ACT (aOR per 10 s, 0.85; 95% CI, 0.72–1.00; $p = 0.048$) were. In a post hoc exploratory evaluation of this model, the overall fit was statistically significant (likelihood-ratio $p = 0.034$; Nagelkerke R^2, 0.062), but discrimination remained

poor (apparent AUC, 0.655; 95% CI, 0.591–0.719; optimism-corrected AUC, 0.596; calibration slope, 0.647). NLR, PLR, and SII did not discriminate patients with an ACT below 400 s (AUC, 0.496, 0.500, and 0.495, respectively), nor did CRP (AUC, 0.533; 95% CI, 0.469–0.596; $p = 0.314$) (Supplementary Table S7). Male sex was associated with a lower likelihood of an ACT below 400 s (aOR, 0.51; 95% CI, 0.30–0.88; $p = 0.015$) and of any additional dose (aOR, 0.62; 95% CI, 0.40–0.95; $p = 0.027$). In the post hoc exploratory analysis that defined inadequate responsiveness using a baseline-adjusted heparin sensitivity index threshold (HSI < 1.0 s/[IU/kg], corresponding to an ACT increase < 300 s; 208 events [32.6%]), the direction of the baseline ACT association reversed (aOR per 10 s, 1.14; 95% CI, 1.01–1.28; $p = 0.035$), while the CRP estimate remained modest (aOR per 5 mg/L, 1.05; 95% CI, 0.99–1.10; $p = 0.087$; log2-CRP aOR per doubling, 1.16; 95% CI, 1.00–1.36; $p = 0.054$).

In a post hoc exploratory model, adding active infection, type of surgery, urgency, and calendar year of surgery (2024 vs. 2023) did not materially change the estimate for CRP in either the prespecified linear model (aOR per 5 mg/L, 1.06; 95% CI, 1.01–1.12; $p = 0.029$) or the log2 model (aOR per doubling, 1.25; 95% CI, 1.06–1.47; $p = 0.007$), and none of the added variables was associated with the outcome ($p = 0.845$, 0.487, 0.967, and 0.335 in the linear model). In post hoc exploratory analyses, restricted cubic splines showed no significant departure from linearity ($p = 0.262$ with 3 knots and $p = 0.341$ with 4 knots), and the overall CRP association in these models was borderline ($p = 0.044$ and $p = 0.068$). The log2 form had the lowest AIC (757.8, vs. 760.2 for linear CRP and 760.9 and 762.0 for the spline models). In a further post hoc exploratory analysis with CRP truncated at its 99th percentile (84.0 mg/L), the aOR per 5 mg/L was 1.09 (95% CI, 1.02–1.15; $p = 0.006$).

3.7. Perfusion Characteristics and Postoperative Outcomes

CPB duration (median, 106 vs. 108 min; $p = 0.734$), aortic cross-clamp time (78 vs. 75 min; $p = 0.552$), lowest hemoglobin, peak lactate, and intraoperative transfusion were similar in the two ACT-response groups (Table 3).

Postoperative outcomes were analyzed as exploratory, non-adjudicated recorded outcomes and are shown in Supplementary Table S2. No robust differences between the ACT-response groups were observed; the only nominal difference, in pulmonary complications (10.2% vs. 5.6%; $p = 0.040$; Fisher exact $p = 0.053$), was one of 15 unadjusted comparisons.

4. Discussion

With one institutional protocol and the same 638 patient-operation records, the observed frequency ranged from 14.1% to 43.6% depending on the definition. Under the primary definition, 176 patients (27.6%) had an arterial-blood ACT below 450 s 3 min after central venous administration of the 300 IU/kg protocol dose. The prespecified multivariable model was not statistically significant as a whole and had poor optimism-corrected discrimination. It identified no reliable routine predictor, and neither the routine laboratory variables collectively nor CRP or the blood count-derived indices individually provided clinically useful discrimination before surgery.

Kim et al. used the same initial dose (3 mg/kg, approximately 300 IU/kg) and the same ACT threshold (< 450 s) in a valve and aortic surgery cohort and reported heparin resistance in 164 of 605 patients (27.1%) [15]. That proportion was closely comparable to the 27.6% observed in our predominantly coronary surgery cohort. Yamashiro et al., who gave 500 IU/kg and required an ACT above 480 s, found 9.7% [13]. A lower initial heparin dose combined with a relatively high ACT target has been suggested as one reason for higher apparent incidence figures [7], and both comparisons are consistent with that explanation.

Knapik et al. applied three definitions to 756 patients undergoing coronary surgery and found incidences of 4.3%, 12.0%, and 64.8% [26]. Their 12.0% came from an ACT below 400 s after 300 U/kg. In our cohort, 90 patients (14.1%) were below 400 s. Raising the threshold to 480 s tripled that number to 278, because 188 patients (29.5%) had values between the two. The multivariable findings also changed with the threshold. At 400 s, CRP was not associated with the outcome (aOR per 5 mg/L, 1.02; 95% CI, 0.95–1.09) and fibrinogen was (aOR per 50 mg/dL, 1.21; 95% CI, 1.08–1.37). The model for this threshold was statistically significant overall (likelihood-ratio $p = 0.034$), unlike the primary model, but its optimism-corrected AUC was 0.596, and NLR, PLR, and SII had AUC values of 0.50 (Supplementary Table S7). With 90 events (7.5 per candidate variable), these estimates are less stable than those of the primary model. A center that targets 400 s would label about half as many patients as one that targets 450 s (14.1% vs. 27.6%) and could find a different set of associated variables, but the absence of clinically useful preoperative discrimination did not depend on the threshold. We could not apply the proposed standard definition, which requires 500 IU/kg [5].

Definitions built on recorded additional heparin depend on what clinicians chose to do. Our records did not separate escalation before CPB from maintenance dosing during it. Forty-one patients whose initial ACT was 450 s or above still received additional heparin. Their CPB was longer than in the 421 patients who received none (median, 125 vs. 105 min), and aortic or other procedures (as categorized in Table 1) were more common (8 of 41 [19.5%] vs. 27 of 421 [6.4%]). Additional dosing in these patients occurred more often during longer and more complex procedures, although its exact indication cannot be determined because dose timing was unavailable.

The prespecified model as a whole was not statistically significant (likelihood-ratio $p = 0.135$), and the study did not identify any reliable routine preoperative predictor of an inadequate initial ACT response. Within that model, the CRP coefficient was nominally significant (aOR per 5 mg/L, 1.06; 95% CI, 1.01–1.12; $p = 0.027$), and a post hoc exploratory log2 transformation gave a similar estimate (aOR per doubling, 1.25; 95% CI, 1.06–1.46; $p = 0.007$; overall likelihood-ratio $p = 0.072$). One nominally significant coefficient among 12 in a non-significant model is compatible with chance, and we regard the CRP finding as hypothesis-generating. Kimura et al. and Kim et al. linked reduced heparin responsiveness to infection [14,15], and CRP was higher in heparin-resistant patients in the cohorts of Kawatsu et al. and Yamashiro et al. [12,13]. Three mechanisms have been proposed: heparin binding to acute-phase plasma proteins [17], neutralization by platelet factor 4 [18], and shortening or distortion of the ACT by an activated inflammatory-coagulation system independently of plasma heparin concentration [7,27]. We measured none of them.

The CRP association had minimal predictive value for individual patients. In post hoc exploratory spline models, the overall association was borderline ($p = 0.044$ and 0.068), and under narrower definitions requiring an ACT below 400 s or a total dose of at least 400 IU/kg, the confidence interval in the prespecified linear model included 1. CRP alone had an AUC of 0.557. The prespecified 12-variable model explained 3.9% of the variation (4.4% in the post hoc exploratory log2 model), and its AUC fell from 0.604 to 0.550 after bootstrap correction (0.606 to 0.555 in the log2 model), with a calibration slope of 0.584 (0.626 in the log2 model). Neither CRP nor the multivariable model can identify individual patients before surgery.

NLR, PLR, and SII did no better than chance, with AUC values between 0.510 and 0.531. Most of our operations were elective, and only 13 patients (2.0%) had an active infection. The cohort provides limited information on patients with infective endocarditis or other overt inflammation.

Platelet count, albumin, and fibrinogen have been reported as predictors [9,11–14]. None was associated with the primary outcome here. Albumin varied little: 55 patients (8.6%) had values of 3.5 g/dL or below, the cut-off used by Chan et al. and Kimura et al. [11,14]. Fibrinogen was associated only with the definition based on an ACT below 400 s (aOR per 50 mg/dL, 1.21; 95% CI, 1.08–1.37), one of several sensitivity models. Kawatsu et al. and Yamashiro et al., who identified fibrinogen, used definitions that selected 5.1% and 9.7% of their cohorts [12,13]. Both are narrower groups than our 27.6%.

Earlier reports linked preoperative heparin therapy to heparin resistance [8–11]. We did not find this association. Only 87 of our patients were unexposed, though, and the confidence interval (aOR, 1.25; 95% CI, 0.73–2.13) leaves room for a clinically relevant effect. We had no record of the type of heparin, its dose, or the time since the last dose. This gap also affects the interpretation of the baseline ACT and of the post hoc exploratory baseline-adjusted HSI. Residual unfractionated heparin from a dose given shortly before the baseline sample would prolong the baseline ACT, reduce the measured ACT increase, and lower the HSI without any true reduction in responsiveness. The absolute post-heparin threshold used for the primary outcome would be shifted in the opposite direction, because a prolonged baseline raises the post-heparin value. Low-molecular-weight heparin prolongs the ACT less than unfractionated heparin, so the size of this distortion would depend on the agent as well as on the interval. In a post hoc exploratory comparison, neither baseline ACT nor the HSI differed between exposed and unexposed patients ($p = 0.941$ and 0.677), and baseline ACT was not correlated with the duration of exposure; these results argue against a large residual effect at the cohort level. With only 87 unexposed patients and no record of the last dose, a residual effect in individual patients cannot be excluded, and the HSI findings should be read with this uncertainty. In 46 patients, Linden et al. found more heparin resistance after preoperative heparin and showed that lower antithrombin did not explain it [28]. Conversely, patients receiving preoperative oral anticoagulants had a lower proportion of an initial ACT below 450 s in unadjusted comparison (13.2% [5 of 38] vs. 28.5% [171 of 600]; $p = 0.040$). This unadjusted comparison was based on only 5 events among 38 exposed patients and should be considered unstable. Of these 38 patients, 23 had also received preoperative unfractionated or low-molecular-weight heparin; their median preoperative INR was 1.06 (IQR, 0.98–1.19), and 2 had an INR above 1.5. The borderline inverse association between baseline ACT and an initial post-heparin ACT below 450 s (aOR per 10 s, 0.89 in the linear model and 0.88 in the log2 model) is partly mechanical because an absolute post-heparin threshold incorporates the starting ACT value; when the outcome was defined by a baseline-adjusted heparin sensitivity index (< 1.0 s/[IU/kg]), the direction of the baseline ACT association reversed (aOR, 1.14; $p = 0.035$).

The exploratory outcome comparisons showed no robust differences between the groups (Supplementary Table S2). The study was sized for the regression model, and with 39 recorded deaths and 14 thromboembolic events, it could not exclude clinically relevant differences in outcome. Knapik et al. reported that mild forms of heparin resistance were not associated with morbidity or mortality, whereas a severe form was associated with death [26]; Kim et al. found more composite complications in resistant patients but no clear difference in individual complications [15].

The results point to a direct implication for the current 300 IU/kg protocol. CRP, NLR, PLR, and SII did not provide clinically useful discrimination before surgery, so preoperative screening with these markers cannot select patients for a higher starting dose or for early supplemental dosing, and even the statistically significant 400 s definition model remained poorly discriminating (optimism-corrected AUC, 0.596). The actionable element of the current protocol is the post-dose ACT measurement itself: an inadequate initial response occurred in more than a quarter of patients at 3 min after the 300 IU/kg dose, and nearly

all of these patients already received additional heparin in practice. Variation in whether additional heparin was given—including the 41 patients with an adequate initial ACT who nonetheless received a further dose (Section 3.2)—suggests that redosing decisions in current practice are not uniformly tied to the 3 min ACT value. A protocol that fixes the supplemental dose and the exact ACT threshold that triggers it would standardize this decision across clinicians and remove any dependence on preoperative risk markers that this study found to be non-discriminating. Whether a standardized redosing step would improve clinical outcomes cannot be determined from this cohort; the exploratory outcome comparisons showed no clear differences between response groups and, with 39 recorded deaths and 14 thromboembolic events, could not exclude clinically relevant effects, so any effect of protocol standardization on outcome would need prospective evaluation.

Limitations

This was a single-center retrospective study based on routine records, and its main limitation is selection. The cohort was a non-consecutive available-record sample of 638 of the 2127 CPB operations performed during the study period (30.0%; quarterly capture, 14.3–57.0%; Supplementary Table S1). Screening was closed in folder batches once the minimum sample size had been exceeded and before any outcome analysis, and the remaining 1489 operations were not assessed for eligibility; this deviated from the protocol-specified consecutive sampling plan. Sampling was non-random and depended on record availability. Aortic operations (5.2% vs. 7.2%) and operations recorded as emergencies (5.3% vs. 10.8%) were underrepresented, the latter partly because emergency operations in which the standard heparinization protocol could not be followed were excluded. The proportion with the primary outcome was similar in 2023 and 2024 (29.2% vs. 26.8%), and adding calendar year to the primary model did not materially change the estimates. Weighting the cohort to the calendar-quarter and surgery-type distribution of all CPB operations gave a similar proportion (27.9%; 95% CI, 23.9–31.8%; Supplementary Table S5). These checks adjust only for measured stratification variables and cannot exclude selection related to unmeasured characteristics. Internal and external validity are both limited: the reported proportions describe this sample and are not incidence estimates for all CPB operations at our center, and the estimated associations between preoperative variables and ACT response may also be biased.

Antithrombin activity is not measured routinely at our center, and anti-Xa assays were unavailable. Antithrombin deficiency is a recognized mechanism of reduced heparin responsiveness [1,2], although resistance also occurs with normal antithrombin activity [15,16]. Without these measurements, we could not separate antithrombin-dependent from antithrombin-independent reduced responsiveness or test whether antithrombin would have improved discrimination, which limits the mechanistic and diagnostic value of the study. ACT has known limitations as a measure of heparin effect [29], and the primary outcome rests on a single arterial whole-blood measurement 3 min after central venous heparin administration. Thirty-six patients (5.6%) had a recorded post-heparin ACT of exactly 450 s, which suggests terminal digit preference at the target value on handwritten perfusion charts; classifying these patients as inadequate responders gave consistent multivariable findings (Section 3.6). Perfusion data were recorded by hand throughout the study period. Electronic perfusion records that capture the ACT directly from the analyzer would remove this source of measurement bias. The initial dose in international units was reconstructed from recorded body weight. Additional heparin given during CPB may have been incompletely recorded: 44 patients without recorded additional heparin had a later ACT below 400 s, so the management-based definitions may underestimate redosing. Details of preoperative heparin therapy (unfractionated vs. low-molecular-weight

heparin, dose, and timing of discontinuation) were unavailable. Laboratory transcription discrepancies identified by the quality-control screen were corrected from the source in 322 records (50.5%) before database lock; a small residual error rate in records that were not individually re-verified cannot be excluded.

We changed the primary definition from the one on the case-report form before analysis because the timing of additional heparin relative to CPB initiation was not recorded, and we added the definition based on an ACT below 480 s after protocol approval but before analysis. The log2 transformation of CRP, the spline and truncation analyses, the ≤450 s and HSI definitions, the extended model, the weighted frequency estimates, the model-fit and discrimination statistics for the 400 s definition, and the comparisons by preoperative heparin exposure were post hoc and exploratory. Internal validation showed substantial model optimism. The model for an ACT below 400 s had 90 outcome events (7.5 per candidate variable) and may yield less stable estimates. EuroSCORE II and left ventricular ejection fraction were not collected, so baseline surgical risk could not be described. Complications were recorded in broad categories without event-specific diagnostic criteria, which prevents direct comparison with studies using standardized definitions (such as KDIGO criteria for acute kidney injury). Thirty-day mortality was a binary case-report-form field with undocumented ascertainment; the observed 6.1% rate is recorded 30-day mortality and not a fully adjudicated estimate. Most patients underwent coronary surgery, and 86.4% had received heparin before the operation; our results may not apply where either is less common.

5. Conclusions

Under the institutional protocol mandating central venous administration of an initial heparin dose of 300 IU/kg, an arterial-blood ACT below 450 s at 3 min was common in this available-record cohort (176 of 638 patients, 27.6%), and additional heparin was recorded in all but one of these patients. The proportion ranged from 14.1% at a 400 s threshold to 43.6% at a 480 s threshold. The prespecified multivariable model was not statistically significant, and none of the routine preoperative variables evaluated in this study, including CRP and the blood count-derived indices, was a reliable predictor or provided clinically useful discrimination before surgery. Under the 400 s definition, the model reached statistical significance, with fibrinogen as the main associated variable, but discrimination remained poor (optimism-corrected AUC, 0.596). Because the cohort was a non-consecutive sample of 30.0% of CPB operations in the study period, these proportions describe this cohort rather than the incidence among all CPB procedures at our center.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/medicina62112286/s1. Table S1: Initial ACT response and recorded additional-heparin groups; Table S2: Adjusted odds ratios (95% CI) from the prespecified 12-variable model under alternative definitions (untransformed C-reactive protein per 5 mg/L); Table S3: Adjusted odds ratios (95% CI) from the 12-variable post hoc exploratory model with log2-transformed C-reactive protein across primary and alternative definitions; Table S4: Cardiac operations with CPB in the study period and patients included in the cohort, by calendar quarter and type of surgery; Table S5: Postoperative outcomes by initial ACT response (exploratory; descriptive, non-adjudicated recorded outcomes); Table S6: Unweighted and weighted frequency of inadequate heparin responsiveness under five definitions (post hoc exploratory); Table S7: Model performance and discrimination of inflammatory markers for a post-heparin ACT below 400 s (post hoc exploratory).

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Medical Sciences Ethics Committee of the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital (protocol code 2024-TBEK 2026/08-21 and date of approval 19 August 2026).

Informed Consent Statement: Informed consent was not obtained because this retrospective study used existing coded records without direct patient contact; the ethics committee approved the study protocol, which did not include an informed consent form (decision no. 2024-TBEK 2026/08-21). The analytic data were de-identified (coded).

Data Availability Statement: The de-identified data set and analysis code supporting the findings of this study are available from the corresponding author upon reasonable request. Public deposition is not permitted because the data derive from patient medical records; access requires approval by the institutional ethics committee to protect patient privacy.

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