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POLYGENIC RISK BURDEN AND THE NARROWING OF THE SAFE OPERATIVE WINDOW IN ACUTE CALCULOUS CHOLECYSTITIS

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Relevance

Emergency cholecystectomy for acute calculous cholecystitis carries a disproportionate share of preventable morbidity in abdominal surgery. Published conversion rates from laparoscopic to open cholecystectomy range from 8% to 22% [1], and are largely determined by whether surgery is performed before or after dense perivesical infiltration has consolidated the tissues of Calot's triangle. Tokyo Guidelines 2018 classify severity at presentation but offer no instrument for predicting how rapidly a given patient's disease will progress to the gangrenous or perforative stage [2]. In clinical practice, this gap is bridged by sequential reassessment, a strategy that works well for the majority but fails for the subset of patients who deteriorate within the first 12 hours of admission.

Accumulated evidence from inflammatory and cardiovascular genetics suggests that susceptibility to rapid tissue injury is partly encoded in the genome. Single-nucleotide polymorphisms in TNF-alpha (rs1800629), TLR4 (rs4986790), IL-6 (rs1800795), SOD2 (rs4880), and VEGFA (rs3025039) collectively modulate the intensity of the innate immune response, oxidative stress, and adaptive angiogenesis, the three processes that determine whether ischaemia of the gallbladder wall remains reversible or progresses to necrosis [3]. No study has examined these five loci jointly in a surgical cholecystitis cohort, and no

quantitative threshold for polygenic risk has been validated against an intraoperative measure of tissue destruction. This gap is the specific motivation for the present work.

Materials and Methods

A prospective-retrospective cohort of 97 patients with acute calculous cholecystitis (Andijan, Fergana, and Namangan branches of the Republican Research Centre for Emergency Medicine, 2021-2025) underwent genotyping by Real-Time PCR (TaqMan assays, Applied Biosystems) for all five loci. Patients were ethnically Uzbek, aged 18 years or older, and admitted as emergencies. Subgroup A comprised destructive forms (gangrenous cholecystitis, empyema, perforated cholecystitis, pericholecystic abscess; n=65, 67.0%) and subgroup B comprised non-destructive forms (catarrhalgic and phlegmonous; n=32, 33.0%), classified by intraoperative and histopathological criteria. A polygenic risk score (PRS) was computed as the simple count of risk alleles carried across all five loci (range 0-5). The primary endpoint was time from symptom onset to intraoperatively confirmed dense pericholecystic infiltrate. Hardy-Weinberg equilibrium was verified by chi-squared test for each locus. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using a dominant inheritance model. ROC analysis quantified the discriminative accuracy of the PRS and of a clinical-laboratory-only score. Surgical outcomes were compared with a historical control group (n=184, 2016-2020) treated under standard protocols. Analyses used SPSS 26.0; two-tailed $p<0.05$ was considered significant.

Results and Discussion

All five loci conformed to Hardy-Weinberg equilibrium ($p>0.05$ for all). Risk allele frequencies were: TNF-alpha GA/AA 59.8%, TLR4 Asp/Gly 37.1%, IL-6 CG/GG 57.7%, SOD2 TC/CC 63.9%, VEGFA CT/TT 53.6%. Co-carriage of

three or more risk alleles was identified in 39 patients (40.2%) and was associated with emergency surgery in 96.2% of cases, compared with 61.5% among patients carrying a single risk allele. This gradient confirms an additive polygenic architecture and distinguishes the present findings from single-gene association studies, whose clinical utility is inherently limited [3].

The most clinically striking observation was the dose-response relationship between PRS and time to pericholecystic infiltrate formation. Patients with PRS=0 showed a mean time of 21.8 hours; PRS=1, 17.3 hours; PRS=2, 11.4 hours; PRS>=3, 6.9 hours ($p<0.001$ across groups). The practical implication is direct: a patient with three or more risk alleles has fewer than seven hours from symptom onset to a tissue barrier that renders laparoscopic dissection hazardous. No clinical criterion available at admission reliably identifies this subgroup [4]. The PRS-based model achieved an area under the ROC curve of 0.974, versus 0.841 for the clinical-laboratory sub-model, a statistically significant increment validating the independent diagnostic contribution of genetic information [5].

Implementation of a personalised surgical algorithm informed by the PRS reduced the postoperative complication rate from 19.4% to 6.2% ($p<0.001$), 30-day mortality from 4.8% to 1.0% ($p<0.05$), and mean hospital stay from 8.4 ± 1.2 to 5.4 ± 0.8 days ($p<0.01$). The conversion rate fell from 12.5% to 3.1% ($p<0.01$), a fourfold reduction attributable to the shift in operative timing: under the personalised protocol, 59.8% of patients underwent urgent cholecystectomy within 12 hours, compared with 18.5% in the historical cohort. These data extend the evidence base for early laparoscopic cholecystectomy [1], demonstrating that optimal benefit is achieved when early surgery is targeted at patients whose molecular profile identifies imminent tissue destruction.

Two caveats are warranted. The PRS constructed here is a simple allele count and does not weight individual loci by their effect sizes, an approach that may

underestimate the contribution of TNF-alpha and TLR4, which showed the largest odds ratios (5.75 and 5.37, respectively). Weighted genetic risk scores [3] represent a methodological refinement that should be explored in validation cohorts. Additionally, the genotyping protocol requires four to six hours in a well-equipped molecular laboratory, which is feasible within a standard emergency admission workflow but may need adaptation in resource-limited settings. The evidence nevertheless supports evaluation of this five-locus panel in prospective randomised trials as a standard adjunct to clinical triage for acute calculous cholecystitis [6].

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