Symposium on Natural and Applied Sciences
Hosted Online from London, United Kingdom
Date: 5th March, 2026
Website: https://econferencia.com

CONVERGENT FAILURE OF INNATE IMMUNITY AND ANTIOXIDANT DEFENCE IN GALLBLADDER EMPYEMA DURING ACUTE CHOLECYSTITIS

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Relevance

Gallbladder empyema, the suppurative form of acute cholecystitis, accounts for a disproportionate share of cholecystitis-related deaths and prolonged hospital admissions [1]. Its pathogenesis converges two overlapping biological failures: inadequate containment of gram-negative bacteria, and impaired cellular resistance to reactive oxygen species generated during ischaemic injury of the gallbladder wall. Toll-like receptor 4 (TLR4) governs bacterial containment through pattern recognition of lipopolysaccharide [2], while mitochondrial superoxide dismutase 2 (SOD2) scavenges superoxide anions at the inner mitochondrial membrane under inflammatory hypoxia [3]. The Asp299Gly missense variant of TLR4 (rs4986790) attenuates NF-kappaB signalling, and the Ala16Val substitution of SOD2 (rs4880) reduces mitochondrial enzyme import by altering the targeting sequence. Each polymorphism individually associates with increased susceptibility to severe inflammatory disease, but their joint clinical effect in the specific setting of biliary empyema has not been investigated in any published cohort to date.

The Fergana Valley of Uzbekistan presents an informative study population for this question. Cholelithiasis prevalence exceeds 18% in adults over 40 years of

age, and patients frequently present late due to delayed care-seeking. Understanding how co-carriage of TLR4 Asp/Gly and SOD2 Val alleles shapes bacteriological outcomes of acute cholecystitis could inform antibiotic selection, surgical planning, and ICU triage in this and comparable emergency surgical settings.

Materials and Methods

The study enrolled 97 patients with acute calculous cholecystitis admitted to three emergency surgical centres in the Fergana Valley (2019-2025). Genotyping of TLR4 Asp299Gly (rs4986790) and SOD2 Ala16Val (rs4880) was performed by Real-Time PCR (TaqMan, Applied Biosystems 7500 Fast) on genomic DNA extracted from peripheral blood. Patients were assigned to three genotype groups: Group I, neither risk allele (TLR4 Asp/Asp and SOD2 TT, n=22); Group II, one risk allele only (n=32); Group III, both TLR4 Asp/Gly and SOD2 TC/CC simultaneously (n=43). Intraoperative bile cultures (2 mL, aerobic and anaerobic) were obtained at cholecystectomy. Blood cultures were drawn within one hour of surgical incision. Gallbladder empyema was defined by macroscopic purulent bile, positive gram-negative culture, and histopathological evidence of transmural suppurative inflammation. Serum malondialdehyde (MDA) at admission served as a surrogate marker of systemic lipid peroxidation [3]. Logistic regression estimated the adjusted effect of genotype group on empyema. Ethics Committee approval: Andijan State Medical Institute, Protocol No. 4/2023.

Results and Discussion

Gallbladder empyema occurred in 4.5% of Group I patients, 21.9% of Group II patients, and 69.8% of Group III patients ($p<0.001$ across groups), demonstrating a compelling additive pattern. Gram-negative bacteraemia was confirmed in

41.9% of Group III versus 13.6% of Group I patients (OR 4.8; 95% CI 1.4-16.4; p=0.01). These bacteriological findings are mechanistically coherent. Arbour N.C. et al. [2] established that TLR4 Asp/Gly carriers generate an attenuated cytokine response to gram-negative lipopolysaccharide; in an obstructed gallbladder, this translates into failure to limit bacterial proliferation before neutrophil recruitment reaches containment levels. The SOD2 Val allele compounds this by permitting accumulation of mitochondrial superoxide, accelerating membrane peroxidation and creating a porous mucosal barrier [3, 4]. Serum MDA at admission was significantly higher in Group III (6.4±1.2 nmol/mL) compared with Group II (4.1±0.9 nmol/mL) and Group I (2.8+/-0.6 nmol/mL) ($p<0.001$). This gradient supports the hypothesis that co-carriage of the SOD2 Val allele is associated with measurably greater systemic oxidative burden at the time of presentation, before any surgical intervention. The adjusted OR for gallbladder empyema in Group III versus Group I was 5.1 (95% CI 1.8-14.6; p=0.002) after controlling for age, sex, diabetes, symptom duration, and fever. The area under the ROC curve for a model combining both genotypes with standard clinical predictors was 0.91, compared with 0.74 for the clinical model alone.

Procalcitonin above 0.5 ng/mL at admission was present in 81.4% of Group III patients and served as a useful clinical correlate for identifying co-carriers in settings where rapid PCR is unavailable. Importantly, among Group III patients, extended-spectrum beta-lactamase producing Enterobacterales accounted for 28% of gram-negative isolates compared with 6% in Group I, a finding with direct implications for empirical antibiotic selection [5]. Current guidelines of Gomi H. et al. [5] recommend gram-negative enteric coverage but do not stratify empirical regimen intensity by host genetic risk; the present data suggest that Group III

carriers may warrant empirical carbapenem or piperacillin-tazobactam initiation before intraoperative culture results are available [6].

References

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