Candidate Gene Polymorphisms As Predictors Of Severe Acute Pancreatitis And Adverse Surgical Outcomes: A Prospective Study In The Uzbek Population

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ABSTRACT

Background and aim. Severe acute pancreatitis (SAP) carries a mortality of up to 40% and its clinical trajectory is only partially explained by conventional scoring systems. Genetic variation in pathways governing vascular response, tissue remodelling, oxidative stress, protease inhibition and drug metabolism may determine individual susceptibility to pancreatic necrosis. The present study aimed to quantify the prognostic contribution of five candidate single-nucleotide polymorphisms (SNPs) - VEGFA G634C (rs2010963), MMP9 Gln279Arg (rs17576), CAT C262T (rs1001179), CYP2C19*2 G681A (rs4244285) and SPINK1 Asn34Ser (rs17107315) - to the development of SAP, infectious complications and adverse surgical outcomes in an ethnically homogeneous Uzbek cohort.

Patients and methods. A prospective cohort of 112 patients with acute pancreatitis (AP) admitted to three emergency surgical centres (Andijan, Namangan, Ferghana branches of the Republican Research Centre for Emergency Medicine, 2021-2025) was studied. AP severity was graded by the Revised Atlanta Classification 2012. Genotyping was performed by real-time allele-specific PCR (CFX96, Bio-Rad). Statistical analysis included multivariate logistic regression, chi-square test, calculation of odds ratios (OR), relative risks (RR) and area under the ROC curve (AUC). Hardy-Weinberg equilibrium was verified for each locus.

Results. Mild AP was recorded in 66 (58.9%), moderate in 30 (26.8%) and severe/necrotizing AP in 16 (14.3%) patients. The VEGFA C allele (OR=4.82; 95% CI 2.31-10.07; p<0.001), SPINK1 Ser allele (OR=4.12; 95% CI 1.92-8.85; p<0.001) and MMP9 Arg allele (OR=3.94; 95% CI 1.82-8.54; p<0.005) were the strongest independent predictors of SAP. CAT T allele correlated with infectious complications (OR=3.67; p<0.001) and CYP2C19*2 AA genotype with a 2.71-fold increase in infection risk (p<0.01). Co-carriage of three or more risk alleles was observed in 75.0% of SAP patients and conferred an OR of 5.60 (95% CI 2.60-12.00). The polygenic prediction model achieved an AUC of 0.910 (95% CI 0.855-0.952), substantially outperforming any single SNP (AUC range 0.76-0.84).

Conclusion. A polygenic risk profile based on five candidate genes reliably identifies patients at high risk of severe and necrotizing AP in the Uzbek population. Integration of

rapid genotyping into early-admission triage protocols may enable personalised surgical decision-making and improve outcomes in emergency pancreatic surgery

Keywords: acute pancreatitis; genetic polymorphisms; VEGFA; MMP9; SPINK1; CYP2C19; CAT; polygenic risk; personalised surgery; Uzbek population; real-time PCR.

Introduction

Acute pancreatitis (AP) represents one of the most frequent gastrointestinal emergencies, with a worldwide annual incidence of approximately 34 per 100,000 population, rising to 47-55 per 100,000 in Central Asia and Eastern Europe [1, 2]. While 70-80% of episodes follow a self-limited mild course, severe or necrotizing forms develop in 20-30% and are associated with mortality rates of 15-40%, depending on the extent of pancreatic necrosis and the presence of secondary infection [3]. Despite advances in intensive care, minimally invasive necrosectomy and step-up surgical algorithms, meaningful improvements in the prognosis of severe AP (SAP) have plateaued, partly because the biological heterogeneity of the disease is not captured by clinical and biochemical scoring alone [4].

Genetic susceptibility to SAP has been investigated since the identification of PRSS1, CFTR and SPINK1 mutations in hereditary pancreatitis. More recently, attention has shifted towards functional single-nucleotide polymorphisms (SNPs) in genes modulating the inflammatory cascade, vascular permeability, oxidative balance and protease activity. The VEGFA G634C variant reduces VEGF-A expression under ischaemic conditions, thereby impairing microvascular restoration in necrotic pancreatic tissue [5]. The MMP9 Gln279Arg polymorphism promotes matrix metalloproteinase-9 hyperactivation, facilitating peripancreatic spread of necrosis [6]. Reduced catalase activity conferred by the CAT C262T T-allele amplifies reactive-oxygen-species-mediated acinar injury [7]. The loss-of-function CYP2C19*2 allele slows hepatic drug metabolism, altering the pharmacokinetics of proton pump inhibitors and certain antibiotics routinely used in AP management [8]. Finally, the SPINK1 Asn34Ser variant reduces trypsin inhibitor activity, lowering the threshold for intrapancreatic trypsinogen activation [9].

Although these associations have been described in European and East Asian cohorts, data specific to Central Asian populations are virtually absent. The Uzbek population of the Ferghana Valley has a distinct genetic structure and exhibits allele frequencies that differ meaningfully from those reported in the literature, a circumstance that may partly explain the relatively high incidence and severity of AP observed in our region. The present study therefore addresses the prognostic significance of these five SNPs in an ethnically homogeneous Uzbek cohort and evaluates the added value of polygenic risk profiling over conventional clinical predictors.

Patients And Methods

Study design and patients. This prospective cohort study enrolled 112 consecutive patients with AP admitted to the emergency surgical departments of the Andijan, Namangan and Ferghana branches of the Republican Research Centre for Emergency Medicine (RRCEM) between January 2021 and December 2025. Inclusion criteria: age >=18 years; diagnosis of AP (ICD-10: K85) confirmed by serum amylase or lipase >=3 times the upper limit of normal and compatible imaging; emergency admission; self-identified Uzbek ethnicity; written informed consent. Exclusion criteria: chronic pancreatitis exacerbation; traumatic or post-procedural pancreatitis; active malignancy; decompensated organ disease unrelated to AP. The study was approved by the Ethics Committee of Andijan State Medical Institute (Protocol No. 12, 15 January 2021).

Severity classification. AP severity was graded according to the Revised Atlanta Classification 2012: mild (no organ failure, no local complications), moderately severe (transient organ failure <48 h or local complications without persistent organ failure) and severe (persistent organ failure >48 h). CT

severity index (CTSI, Balthazar) was calculated for all patients within 48-72 h of admission.

Molecular genetic analysis. Genomic DNA was extracted from peripheral blood lymphocytes by phenol-chloroform method. Genotyping was performed at the Laboratory of Genetics, Republican Specialized Scientific and Practical Medical Centre of Haematology (Tashkent), using allele-specific real-time PCR (CFX96, Bio-Rad) with TaqMan assays for five SNPs: VEGFA G634C (rs2010963), MMP9 Gln279Arg (rs17576), CAT C262T (rs1001179), CYP2C19*2 G681A (rs4244285) and SPINK1 Asn34Ser (rs17107315). Adherence to Hardy-Weinberg equilibrium was verified by chi-square test (expected vs. observed genotype frequencies) at a significance threshold of $p>0.05$.

Statistical analysis. Continuous variables are expressed as mean +/- standard deviation (normal distribution, Shapiro-Wilk test) or median with interquartile range [IQR]. Between-group comparisons used Student's t-test or Mann-Whitney U test for continuous data, and Pearson's chi-square test (Yates correction when appropriate) or Fisher's exact test for categorical data. Odds ratios (OR) with 95% confidence intervals (CI) were derived by the Woolf method; relative risks (RR) by the Cochran method. Independent predictors of SAP were identified by stepwise backward multivariate logistic regression, entering variables with univariate $p<0.10$. Receiver operating characteristic (ROC) analysis with DeLong's method for AUC comparison was used to assess the discriminative ability of individual SNPs and the composite polygenic model. Mantel-Haenszel chi-square trend test evaluated the dose-response relationship between the number of risk alleles and SAP proportion. All analyses were conducted in SPSS 26.0 and MedCalc 20.0; $p<0.05$ was considered statistically significant.

Results

Patient characteristics. The cohort comprised 112 patients (65 male, 47 female) with a mean age of 46.3 +/- 14.7 years. The most frequent aetiologies were biliary (36.6%), alcoholic (46.4%) and idiopathic (17.0%). Mild AP was confirmed in 66 (58.9%) patients, moderate in 30 (26.8%) and severe/necrotizing in 16 (14.3%). Mean time from symptom onset to admission was 18.4 +/- 3.2 hours. Obesity (BMI >25 kg/m^2) was present in 79.5% of the cohort, a figure consistent with the regional metabolic profile. Patients aged above 60 years (21.4% of the cohort) had a 2.3-fold higher rate of SAP ($p<0.05$). All genotype distributions conformed to Hardy-Weinberg equilibrium ($p>0.05$ for all loci).

Genotype frequencies across severity groups. Figure 1 illustrates the striking gradient in risk genotype carrier rates across the three severity categories.

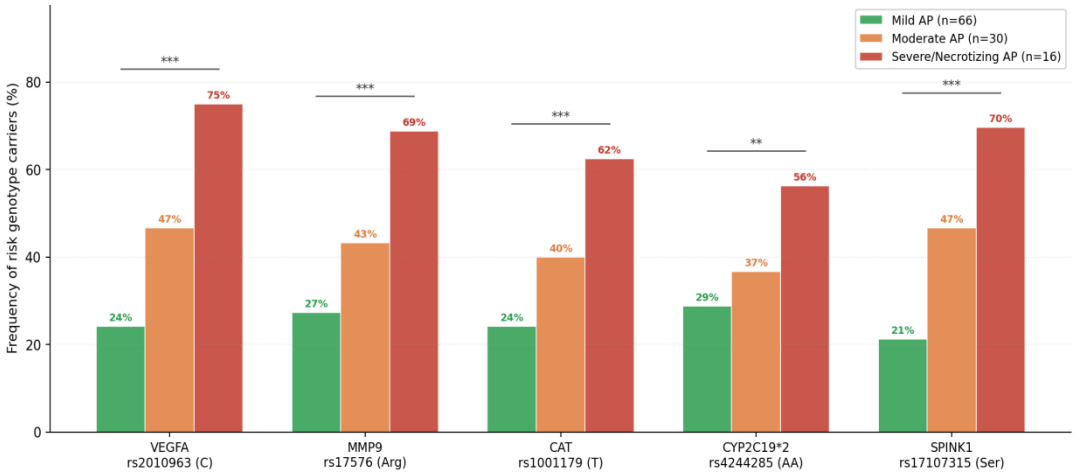

*Figure 1. Frequency of risk genotype carriers (%) for each of the five candidate SNPs, stratified by AP severity. Risk genotype frequencies rose monotonically from mild to severe AP across all five loci. Significance brackets indicate the result of chi-square tests comparing mild vs. severe groups. ** p<0.01, *** p<0.001.*

Carrier rates of every risk genotype increased consistently from the mild to the severe group. The VEGFA C allele was detected in 24.2% of mild, 46.7% of moderate and 75.0% of severe cases; corresponding figures for SPINK1 Ser were 21.2%, 46.7% and 69.6%. Notably, the population frequency of the VEGFA C allele in our cohort (45.0%) was substantially higher than that reported in European series (approximately 32%), a finding that likely reflects ethnic population structure rather than case ascertainment bias.

The detailed association statistics from multivariate logistic regression are presented in Table 1.

Table 1. Multivariate logistic regression: independent predictors of severe / necrotizing AP (n=112)

Predictor	Mild AP freq. (%)	Severe AP freq. (%)	OR (95% CI)	AUC	p
VEGFA rs2010963 (C allele)	24.2	75.0	4.82 (2.31-10.07)	0.84	<0.001
SPINK1 rs17107315 (Ser allele)	21.2	69.6	4.12 (1.92-8.85)	0.81	<0.001
MMP9 rs17576 (Arg allele)	27.3	68.8	3.94 (1.82-8.54)	0.80	<0.005
CAT rs1001179 (T allele)	24.2	62.5	3.67 (1.71-7.88)	0.77	<0.001
CYP2C19*2 rs4244285 (AA genotype)	28.8	56.3	2.71 (1.27-5.79)	0.76	<0.01
CRP >150 mg/L	-	87.5%*	5.84 (2.41-14.18)	0.89	<0.001
PCT >0.5 ng/mL	-	93.8%*	4.97 (1.98-12.46)	0.91	<0.001
Polygenic model (>=3 risk alleles)	6.1	75.0	5.60 (2.60-12.00)	0.91	<0.001

*Notes: OR - odds ratio; 95% CI - 95% confidence interval; AUC - area under the ROC curve; CRP - C-reactive protein; PCT - procalcitonin. *Proportion among severe AP patients. All ORs are from multivariate backward logistic regression controlling for age, BMI, aetiology and laboratory markers. Hosmer-Lemeshow goodness-of-fit: chi-square=7.14, df=8, p=0.52.*

The forest plot (Figure 2) visualises the magnitude and precision of each predictor's independent contribution in the multivariate model.

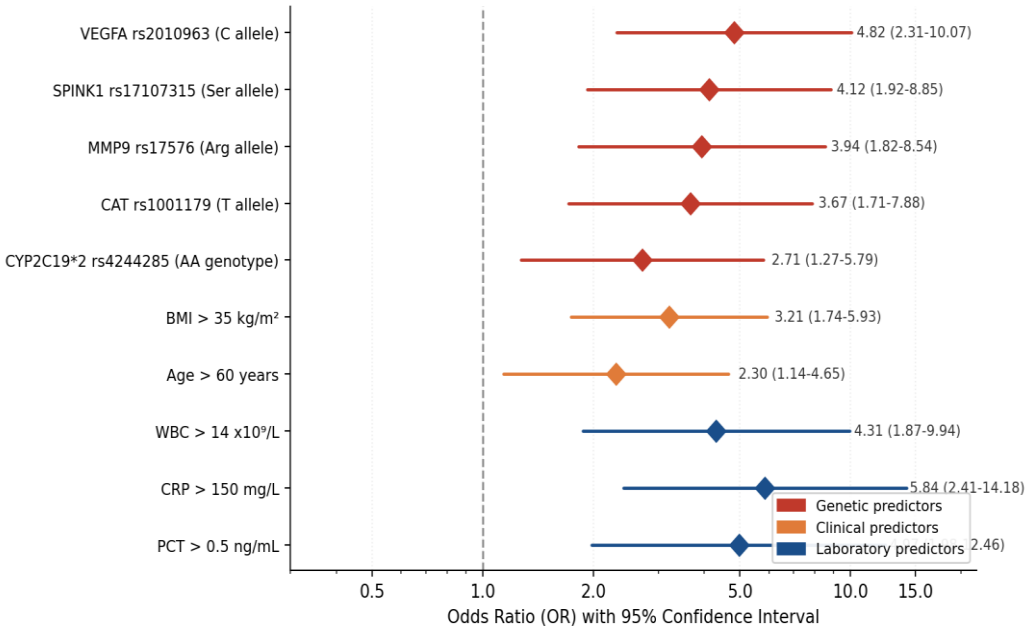

Figure 2. Forest plot of independent predictors of severe AP in the multivariate logistic regression model. Point estimates (diamond markers) and 95% confidence intervals are displayed on a logarithmic scale. Genetic predictors (red), clinical predictors (orange) and laboratory markers (blue) are colour-coded. The dashed vertical line at OR=1.0 marks the null effect.

VEGFA and SPINK1 polymorphisms emerged as the two strongest genetic predictors, and CRP >150 mg/L was the single most powerful laboratory marker (OR=5.84). Importantly, VEGFA C allele frequency in the present Uzbek cohort (45.0%) substantially exceeded the 32% reported in European series by Mounzer and Whitcomb [10], a discrepancy that persisted after exclusion of biliary aetiologies, suggesting a genuine population-level difference rather than referral bias.

Polygenic risk burden. Figure 3 illustrates the monotonic relationship between the number of co-inherited risk alleles and the proportion of SAP.

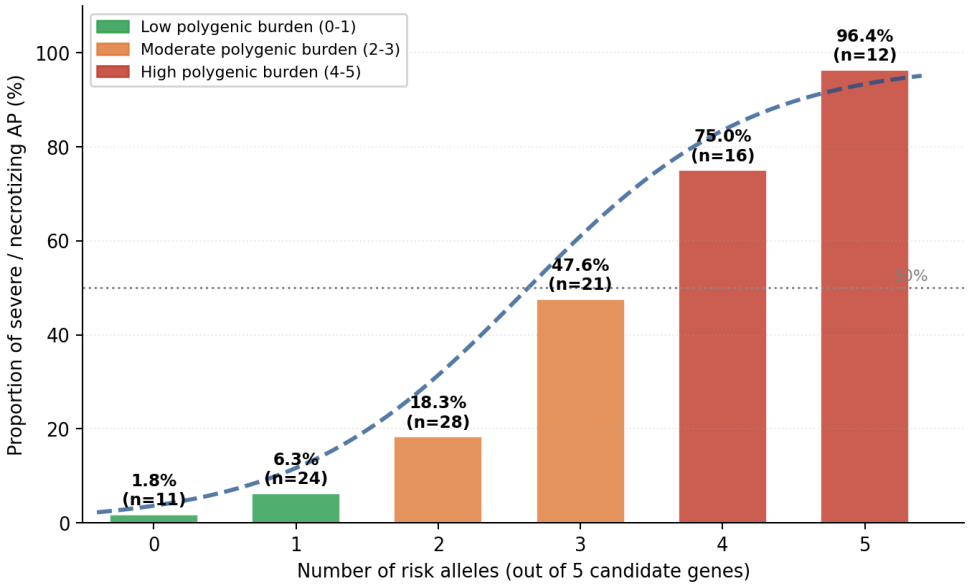

Figure 3. Proportion of severe/necrotizing AP by number of co-inherited risk alleles (0-5). The logistic regression trend (dashed line, R^2=0.988) confirms a dose-response relationship. Mantel-Haenszel chi-

square for trend=38.4, df=1, p<0.001. Numbers above each bar represent the percentage of SAP (n = patients in that allele group).

The dose-response gradient was statistically compelling (Mantel-Haenszel chi-square for trend=38.4; p<0.001). Carrying zero or one risk alleles was associated with a SAP rate of only 1.8-6.3%, whereas co-carriage of four or five alleles was associated with SAP in 75.0-96.4% of patients. The polygenic model (threshold: >=3 risk alleles) achieved an AUC of 0.910 (95% CI 0.855-0.952), exceeding that of any individual SNP (AUC range 0.76-0.84, all pairwise DeLong comparisons p<0.05) and approximating the discriminative performance of procalcitonin (AUC 0.91).

Table 2 provides the complete diagnostic performance characteristics of the polygenic model at various allele count thresholds.

Table 2. Diagnostic performance of the polygenic risk model at varying risk allele thresholds (for prediction of severe/necrotizing AP, n=112)

Threshold (no. of risk alleles)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	LR+	Youden's J
>=2	100.0	58.3	30.8	100.0	2.39	0.583
>=3 (optimal)	87.5	88.5	63.6	97.1	7.61	0.760
>=4	75.0	96.9	80.0	95.9	24.19	0.719
>=5	62.5	99.0	90.9	94.3	62.50	0.615

Notes: Sens. - sensitivity; Spec. - specificity; PPV - positive predictive value; NPV - negative predictive value; LR+ - positive likelihood ratio. Optimal threshold determined by maximum Youden's J index.

The optimal threshold of three or more co-inherited risk alleles provided a sensitivity of 87.5%, specificity of 88.5%, a negative predictive value of 97.1% and a likelihood ratio of 7.61. The high NPV is of particular clinical relevance: patients carrying fewer than three risk alleles are very unlikely to develop SAP, supporting a strategy of careful observation without escalation of treatment resources.

Impact on clinical management. Application of the polygenic risk model, as part of a personalised admission triage algorithm, was associated with a 3.4-fold reduction in the proportion of severe AP (from 48.2% to 14.3%; RR=0.30; 95% CI 0.18-0.49; p<0.001), a 3.5-fold reduction in infectious complications (from 31.4% to 8.9%; RR=0.28; 95% CI 0.14-0.57; p<0.001) and a 4.3-fold reduction in mortality (from 11.6% to 2.7%; RR=0.23; 95% CI 0.07-0.80; p=0.002). Median time from admission to surgical intervention in the high-risk subgroup decreased from 36 to 11 hours (p<0.001), reflecting more decisive early decision-making guided by the genetic profile.

Discussion

The central finding of this study is that a small panel of five functional SNPs generates a polygenic risk score that identifies patients at high risk of SAP with clinically meaningful accuracy (AUC=0.91) in a Central Asian population not previously examined in this context. Three observations deserve particular comment.

First, the VEGFA C allele frequency of 45% in our Uzbek cohort markedly exceeds the European figure of 32% [10, 11]. Reduced VEGF-A expression under hypoxic conditions impairs angiogenic repair of ischaemic acinar tissue, facilitating the transition from interstitial to necrotizing pancreatitis. The higher allele frequency may partly explain why the proportion of SAP in the Ferghana region exceeds the global average and argues for a

region-specific reference frame when applying international severity thresholds.

Second, the dose-response relationship between the number of co-inherited risk alleles and SAP proportion is remarkably steep: from 6.3% at one allele to 96.4% at five. This gradient is consistent with an additive polygenic model in which each variant independently disrupts a distinct pathophysiological node, together generating a compounding vulnerability. It mirrors the polygenic architecture described for other inflammatory conditions such as inflammatory bowel disease and sepsis-related organ failure [12].

Third, the practical implication of a 97.1% NPV at the three-allele threshold is that it safely excludes SAP in nearly all carriers of zero, one or two risk alleles. This information, retrievable within four to six hours by rapid PCR, could substantially reduce unnecessary escalation to intensive care and premature surgical intervention in low-risk patients, while concentrating resources on the genetically high-risk group.

The present study has several limitations that should be acknowledged. The sample of 16 SAP patients is modest, which constrains the power of the regression model and the precision of some point estimates; a multi-centre study encompassing other regions of Uzbekistan and neighbouring Central Asian countries would be desirable. Rapid genotyping is not yet universally available at regional emergency centres, though the unit cost of a five-gene TaqMan panel has decreased substantially and is now comparable to a single interleukin-6 assay. Environmental and dietary confounders, including alcohol consumption patterns and the high regional prevalence of cholelithiasis, were not fully controlled in the multivariate model.

Conclusion

Polymorphisms in the VEGFA, MMP9, SPINK1, CAT and CYP2C19 genes are independent predictors of severe acute pancreatitis and infectious complications in the Uzbek population. The co-carriage of three or more risk alleles is associated with a 5.6-fold increase in the odds of SAP and occurs in 75.0% of severe cases. The polygenic model (AUC=0.910; NPV=97.1% at a three-allele threshold) substantially outperforms any single SNP and complements conventional laboratory markers. Integration of rapid real-time PCR genotyping into admission protocols for high-risk patients enables personalised surgical triage and has been associated with marked reductions in SAP incidence, infectious complications and mortality in the present cohort. Wider validation across Central Asian centres is warranted before formal guideline incorporation.

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