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Original article

Effect of HMGB1 gene polymorphisms on AMPK and HMGB1 levels in neonatal sepsis

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Abstract. *Background and aim:* Neonatal sepsis is a major cause of morbidity and mortality, influenced not only by infection but also by genetic and immune responses. High Mobility Group Box 1 (HMGB1) acts as a late pro-inflammatory mediator, while AMP-activated protein kinase (AMPK) regulates cellular energy. We examined whether single-nucleotide polymorphisms (SNPs) in the HMGB1 gene affect HMGB1 and AMPK levels in neonates with sepsis. *Methods:* Ninety-nine neonates were studied: 51 with sepsis, 18 with congenital pneumonia, and 30 healthy controls (34–42 weeks). HMGB1 sequencing identified SNPs (rs3742305/COSV58104338, rs2249825, rs41376448, rs1060348). Plasma HMGB1 and AMPK were measured by ELISA on day 2 of admission. Clinical data (CRP, procalcitonin, blood cultures) were collected. Infants were analyzed by genotype (wild type, heterozygous, homozygous) and cumulative SNP count. *Results:* SNP frequency was higher in sepsis (52.9%) than in pneumonia (27.8%); homozygous variants occurred only in sepsis ($p < 0.05$). On day 2, HMGB1 and AMPK were lower in sepsis versus pneumonia (1510 ± 411 vs. 1709 ± 422; 1132 ± 401 vs. 1485 ± 401). For rs3742305, homozygotes had higher HMGB1 and heterozygotes reduced AMPK. For rs2249825, homozygotes showed the highest HMGB1 and lowest AMPK; heterozygotes also had reduced AMPK. Rs41376448 showed a similar pattern, while rs1060348 was not significant. With increasing SNPs (1–4), AMPK declined progressively ($p < 0.05$), while HMGB1 trended upward. *Conclusions:* HMGB1 polymorphisms, particularly rs3742305, rs2249825, and rs41376448, are linked to altered HMGB1 and AMPK in neonatal sepsis. The cumulative SNP load predicts greater metabolic dysregulation, suggesting HMGB1 genotyping may aid risk stratification and personalized therapy. (www.actabiomedica.it)

Key words: neonatal sepsis, HMGB1, AMPK, gene polymorphism, SNP, biomarker

Introduction

Neonatal sepsis, typically occurring within the first days to hours of life, constitutes a major global health problem. Because the neonatal immune system is immature, neonates are highly vulnerable to systemic infection and widespread inflammation. Sepsis can rapidly progress to multi-organ dysfunction and death (1). Early diagnosis and risk stratification are critical, yet currently available biomarkers and clinical scoring systems are imperfect. High Mobility Group Box 1 (HMGB1) is a nonhistone chromosomal protein that normally resides in the nucleus, regulating DNA architecture and gene transcription. Under stress or injury, HMGB1 can translocate to the extracellular milieu, where it acts as a Damage-Associated Molecular Pattern (DAMP), engendering inflammatory signaling through receptors such as RAGE (receptor for advanced glycation end products) and Toll-like receptors. Elevated HMGB1 levels have been implicated in sepsis severity and poor outcomes in adults and children (2–5). AMP-activated protein kinase (AMPK)

is a conserved serine/threonine kinase that senses cellular energy status. When the AMP/ATP ratio increases (i.e., energy deficiency), AMPK is activated to promote catabolic pathways and inhibit anabolic ones, restoring energy balance. In immune cells, AMPK also modulates inflammatory responses, autophagy, and oxidative stress. In sepsis, metabolic dysregulation can impair AMPK signaling, exacerbating cellular damage. Interindividual variability in sepsis susceptibility, severity, and outcomes cannot be solely attributed to pathogen factors (6–9). Host genetics plays a substantial role, with single-nucleotide polymorphisms (SNPs) modulating the expression or function of immune and metabolic genes (10). Identifying SNPs that influence biomarkers such as HMGB1 and AMPK may reveal mechanistic insights and potential precision medicine strategies.

Aims of this study

We hypothesized that functional SNPs in the HMGB1 gene may influence circulating HMGB1 concentrations and, indirectly, the metabolic regulator AMPK during neonatal sepsis. Our primary objective was to compare plasma HMGB1 and AMPK levels across genotype groups in neonates with sepsis. A secondary aim was to examine whether the cumulative number of SNPs bears a relationship with biomarker derangements.

Patients and Methods

Study design and participants

This was a prospective cohort study conducted in Baku, Azerbaijan. We enrolled 69 neonates admitted to the Neonatal Intensive Care Unit (NICU) with suspected sepsis, plus 30 healthy newborns as controls (total n = 99). Among the 69, 51 were ultimately confirmed to have clinical sepsis (Group I), while 18 were diagnosed with congenital pneumonia (Group II). Infants in the control group were recruited from the Azerbaijan Scientific Research Institute of Obstetrics and Gynecology.

Inclusion criteria:

1. Gestational age between 34 and 42 weeks
2. Clinical suspicion of sepsis
3. Informed written parental consent

Exclusion criteria:

- Major congenital anomalies
- Gestational age < 34 or > 42 weeks
- Lack of parental consent

Clinical and laboratory assessment

Upon admission, the infants underwent routine laboratory and instrumental evaluation, including complete blood count, C-reactive protein (CRP), procalcitonin (PCT), blood cultures, arterial blood gas, and acid-base balance. Diagnosis of sepsis was made according to the European Medicines Agency (EMA) sepsis scoring criteria, requiring at least two clinical and two laboratory markers consistent with infection.

Although the study was prospectively registered and all neonates were consecutively enrolled at admission, the present analysis represents a cross-sectional comparison nested within that observational cohort. Biomarker (HMGB1, AMPK) and genotype data were obtained at a single, predefined time point — within the first 48 hours of life or within 24 hours after NICU admission. Early-onset sepsis (EOS) was defined as sepsis diagnosed ≤ 72 hours after birth, while late-onset sepsis (LOS) was defined as sepsis diagnosed > 72 hours. Pneumonia cases were identified at admission by radiologic and clinical findings consistent with congenital infection; sampling for biomarker and genetic analysis was performed prior to antibiotic therapy. Thus, the design is best described as a cross-sectional case–control comparison (sepsis vs pneumonia vs controls) nested in a prospective observational cohort of NICU admissions. A 2 mL venous blood sample was obtained in EDTA tubes for genetic studies. On day 2 of admission, separate plasma samples were collected for measurement of HMGB1 and AMPK concentrations using ELISA kits (Shanghai Coon Koon Biotech Co., Ltd), according to manufacturer instructions.

Genetic analysis and SNP identification

Genomic DNA was extracted and HMGB1 gene sequencing was performed using next-generation sequencing (NGS). Briefly:

1. PCR amplification of the HMGB1 gene (primers synthesized in-house) using Nippon FastGene Optima HotStart Ready Mix
2. Agarose gel electrophoresis (0.2% agarose, stained with MIDORI Green Advance) to confirm PCR products
3. Library preparation with Illumina DNA Prep Kit
4. Sequencing on the Illumina NovaSeq 6000 platform
5. Classification of genotypes as wild type, heterozygous, or homozygous variant

Statistical analysis

Data were processed using SPSS version 29. Newborns were grouped by genotype for each SNP, and also stratified by the total count of identified SNPs (1, 2, 3, or 4). Continuous data (e.g., HMGB1, AMPK) were presented as mean ± standard deviation (SD) with 95% confidence intervals (CI). Categorical data were compared by chi-square tests. Between-group comparisons (e.g., biomarker levels by genotype) utilized t-tests or ANOVA, with $p < 0.05$ considered statistically significant.

Results

The results of the genetic variations (SNVs) in all examined newborns are presented in Table 1.

Because all participants carried the rs1929606 variant, this SNP was excluded from comparative analyses.

Distribution of genetic polymorphisms by clinical group

Among all 99 neonates studied, HMGB1 SNPs were significantly more prevalent in the sepsis group (Group I) compared to the pneumonia group (Group II) and controls. Specifically:

- 52.9% of septic infants had one or more of the studied HMGB1 SNPs.
- 27.8% of pneumonia cases exhibited SNPs (Table 2).

We conducted additional per-SNP Pearson Chi-Square exact tests and observed that rs3742305 and rs2249825 were more frequent in the sepsis group ($p<0,05$). Notably, homozygous variants were exclusively found in the sepsis group — suggesting a potential role in disease severity or susceptibility. The pattern of SNV counts varies slightly between groups: Group II (likely congenital pneumonia) had the highest proportion of individuals with only 1 SNV (72.2%), suggesting fewer mutations overall. Group I (clinical sepsis) and the Control group had more individuals with multiple SNVs (especially 4 SNVs: 37.3% and 30%, respectively). However, these differences are not statistically significant, meaning that the number of SNVs detected does not differ meaningfully between sepsis, pneumonia, and healthy neonates and SNV burden alone likely does not distinguish affected from healthy neonates in this dataset.

Clinical characteristics and baseline comparisons

No statistically significant differences were observed in gestational age or birth weight between groups:

- Sepsis group: 3059 ± 411 g; 36.9 ± 2.0 weeks gestation
- Pneumonia group: 3039 ± 604 g; 36.8 ± 2.1 weeks
- Control group: 3117 ± 314 g; 37.9 ± 1.03 weeks

This parity eliminates confounding due to prematurity or growth restriction and strengthens the case for genetic factors playing a key role.

PCT and CRP Trends as Sepsis Biomarkers

Table 1. HMGB1 gene variations in several positions of 99 newborns

HMGB1 SNVs	Ref, alt, allele	consequence	impact	Bio-type	Variant-class	Amino acid	codon	Zyg
rs1929606 n=99	A, G, G	synonimous	low	Protein-coding	SNV	Y	taT/taC	homo
rs3742305& COSV58104338, n=33	C, G, G	intron	modifier	Protein-coding	SNV	null	null	Hom, Het
rs2249825 n=32	G, C, C	intron	modifier	Protein-coding	SNV	null	null	Hom, Het
rs41376448 n=33	G,GA,A	3_prime_UTR_	modifier	Protein-coding	insertion	null	null	het
rs1382808052 n=1	CCT, C, (-)	intron	modifier	Protein-coding	deletion	null	null	het
rs139424505 n=1	T,G,G	missense	modereta	Protein-coding	SNV	K/Q	Aag/Cag	het
rs370567500 n=2	A, G, G	splice_ polypyrimidine_ tract and intron	low	Protein-coding		null	null	het
rs758886824 n=1	ATCT, A,(-)	İnframe_deletion	modereta	Protein-coding	deletion	ED/D	gaAGAt/ gat	het
rs1060348 n=9	G,A,A	synonimous	low	Protein coding	SNV	F	ttC/ttT	het
rs1255635291 n=1	TG,T,(-)	intron	mofifier	Protein coding	deletion	null	null	het
rs58468031 n=1	CT, C, (-)	3_prime_UTR_ variant	modifier	Protein_coding	deletion	null	null	hom

Table 2. The count of SNVs in groups

Groups	SNVs counts					
	1	**2**	**3**	**4**	**5**	
I group	23 (45,1%)	7 (13,7%)	1 (2%)	19 (37,3%)	1 (2%)	Pearson Chi-square value=7,091 *p=0,527* Likelihood ratio value=8,255 *p=0,409*
II group	13 (72,2%)	3 (16,7%)	0	2 (11,1%)	0	
Control group	14 (46,7%)	6 (20%)	1 (3,3%)	9 (30%)	0	

CRP and procalcitonin were measured both at birth and on admission to NICU:

- PCT on admission was significantly elevated in the sepsis group.
- CRP values were highest in the sepsis group on day 2 (Table 3).
- Correlation between PCT levels and sepsis outcomes:
- PCT < 0.5 μg/L: 80% developed sepsis
- PCT 0.5–2 μg/L: 50% developed sepsis
- PCT > 2 μg/L: 86% developed sepsis

($\chi^2 = 7.23$, $p = 0.027$)

However, PCT and CRP did not vary significantly by SNP genotype, suggesting that these inflammatory markers are driven more by infection dynamics than by host genetics.

HMGB1 and AMPK Biomarker Levels by Group

Table 3. Comparison of Laboratory Parameters Between Groups on the 1st and 2nd Days

Laboratory parameters*	Groups	N	Mean	Std. Deviation	Std. Error Mean	Levene's Test for Equality of Variances		T-test for equality of means
						F	Sig.	Sig(two-sided)
PCT	pneumonia	14	4.95	6.27	1.67	4.86	.031	**.015**
	sepsis	51	12.38	17.56	2.46			
WBC	pneumonia	42	14.53	5.14	0.79	3.27	.073	**.415**
	sepsis	84	17.32	21.74	2.37			
PLT	pneumonia	42	284.02	126.53	19.52	0.58	.446	**.049**
	sepsis	84	239.18	100.31	10.94			
Lym	pneumonia	42	3.83	2.06	0.32	0.96	.330	**.574**
	sepsis	74	4.11	3.35	0.39			
Neutrophil	pneumonia	42	8.69	4.27	0.66	1.59	.210	**.862**
	sepsis	73	8.87	6.98	0.82			
Lactate	pneumonia	22	1.77	0.87	0.19	5.72	.019	**.001**
	sepsis	72	3.02	2.05	0.24			
Fibrinogen	pneumonia	43	124.70	122.89	18.74	0.22	.644	**.068**
	sepsis	80	167.80	124.76	13.95			
ALT	pneumonia	9	12.46	3.96	1.32	1.72	.197	**.102**
	sepsis	31	46.03	110.58	19.86			
Albumin	pneumonia	7	9.37	11.41	4.31	0.09	.772	**.993**
	sepsis	44	9.33	11.53	1.74			
CRP 1st day	pneumonia	28	9.63	15.55	2.94	2.02	.158	**.178**
	sepsis	74	16.71	37.14	4.32			
CRP 2nd day	pneumonia	38	9.05	15.27	2.48	18.55	.001	**.001**
	sepsis	83	34.09	51.35	5.64			

PCT-procalcitonin (ng/ml), WBC-white blood cell (10^3/μL), PLT-platelet (*10^3/μL), lymphocyte(*10^3/μL), neutrophil (*10^3/μL), lactate (mmol/L), Fib-Fibrinogen (mg/dL), ALT-alanine aminotransferase (U/L), albumin g/dL, CRP-C reactive protein mg/L.

When comparing plasma levels of biomarkers between sepsis and pneumonia:

- HMGB1:
  - Sepsis group: 1510 ± 411 pg/mL (95% CI: 1400–1620)
  - Pneumonia group: 1709 ± 422 pg/mL (95% CI: 1546–1874)
- AMPK:
  - Sepsis group: 1132 ± 401 pg/mL (95% CI: 1025–1240)
  - Pneumonia group: 1485 ± 401 pg/mL (95% CI: 1308–1662)

Both biomarkers were significantly lower in the sepsis group, suggesting consumption or dysregulation of inflammatory and energy response pathways.

The effects of the rs3742305 / COSV58104338 polymorphism on HMGB1 and AMPK levels are shown in Figures 1, 2, 3, 4.

HMGB1 Levels:

- No significant difference was observed in heterozygous carriers vs. wild types.
- Homozygous carriers, however, had significantly higher HMGB1 levels ($p < 0.05$), implying gene dosage effects on expression.

AMPK Levels:

- Heterozygous carriers of rs3742305 exhibited significantly reduced AMPK levels compared to non-carriers ($p < 0.05$).

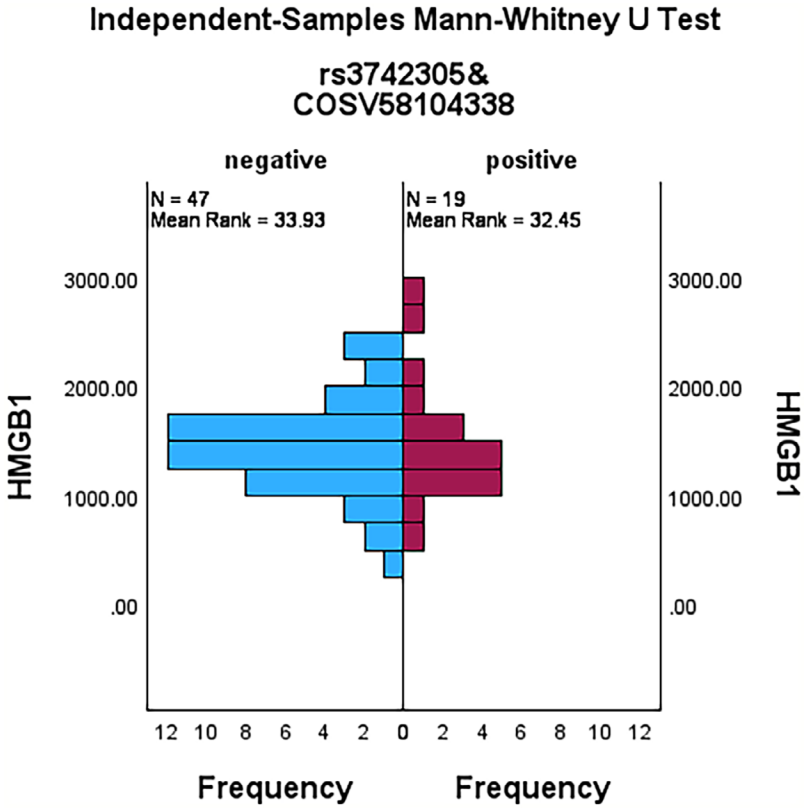

Figure 1. HMGB1 concentration (pg/mL) based on SNV rs3742305and-COSV58104338 (+/–) status.

- Suggests that even a single variant allele can disrupt metabolic signaling.

This highlights rs3742305 as a functionally relevant SNP, influencing both immune and metabolic parameters. For rs2249825, the effects on biomarker levels are shown in Figures 5, 6, 7, and 8.

- HMGB1:
  - Homozygous > Heterozygous > Wild type
  - Significant difference between homozygotes and others ($p < 0.05$)

- AMPK:
  - Homozygous carriers had the lowest levels
  - Even heterozygotes had significantly reduced AMPK

For rs41376448:

- Only heterozygous forms were detected.
- These carriers showed increased HMGB1 and reduced AMPK, consistent with other SNPs.
- Together, both SNPs demonstrate a convergent pattern:
- Elevated HMGB1 (inflammation)
- Reduced AMPK (metabolic stress)

This suggests that multiple HMGB1 SNPs may synergistically contribute to immune overactivation and energy dysregulation.

rs1060348: A Non-Functional Variant?

Unlike other SNPs:

- No significant differences in either HMGB1 or AMPK levels were observed in rs1060348 carriers.

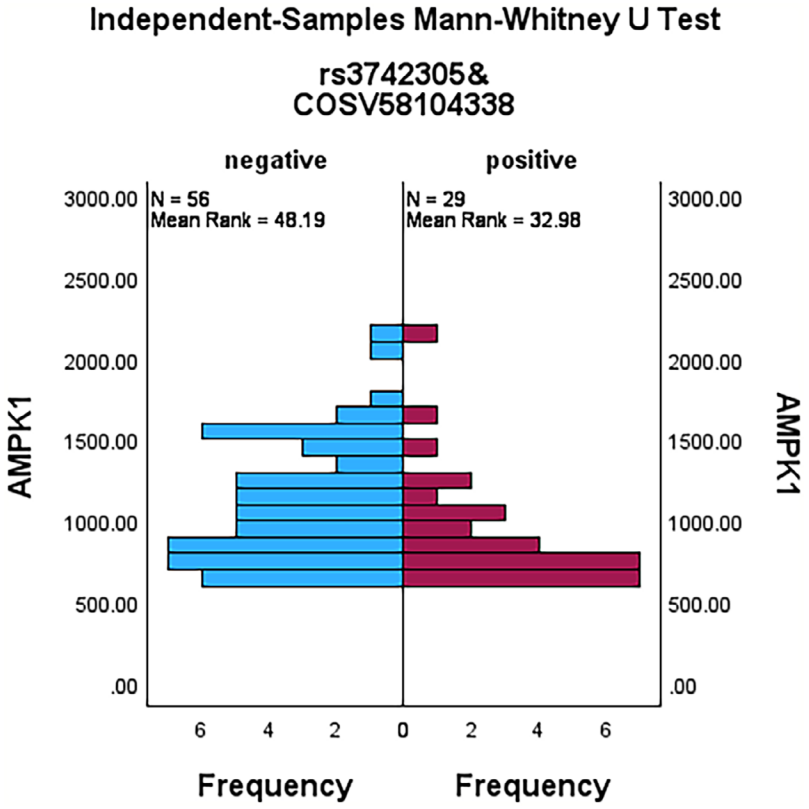

Figure 2. AMPK concentration (pg/mL) based on SNV rs3742305and-COSV58104338 (+/–) status.

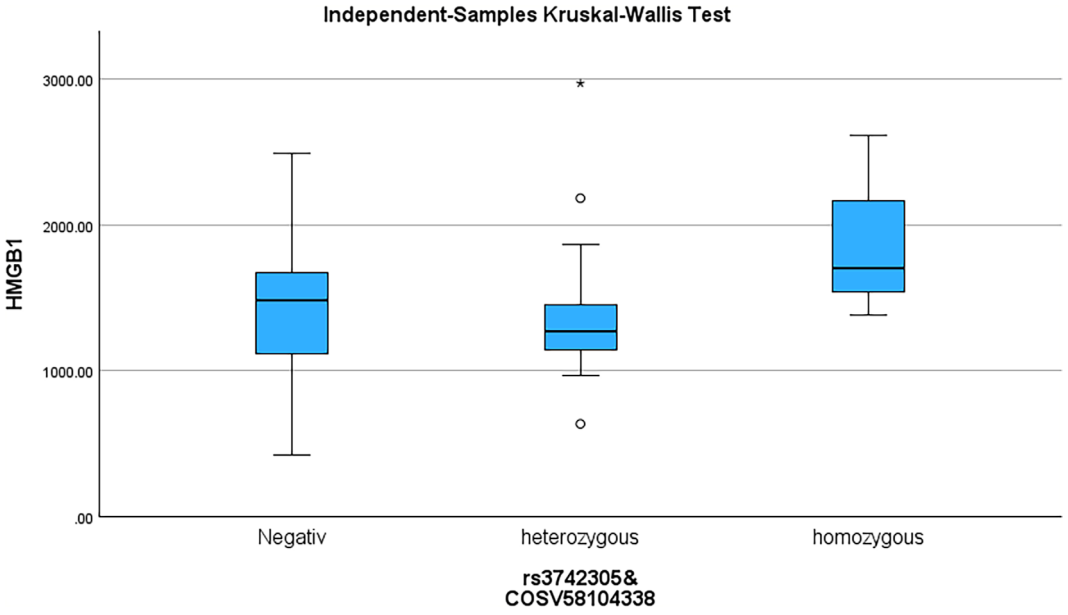

Figure 3. HMGB1 concentration based on SNV rs3742305andCOSV58104338 allele form.

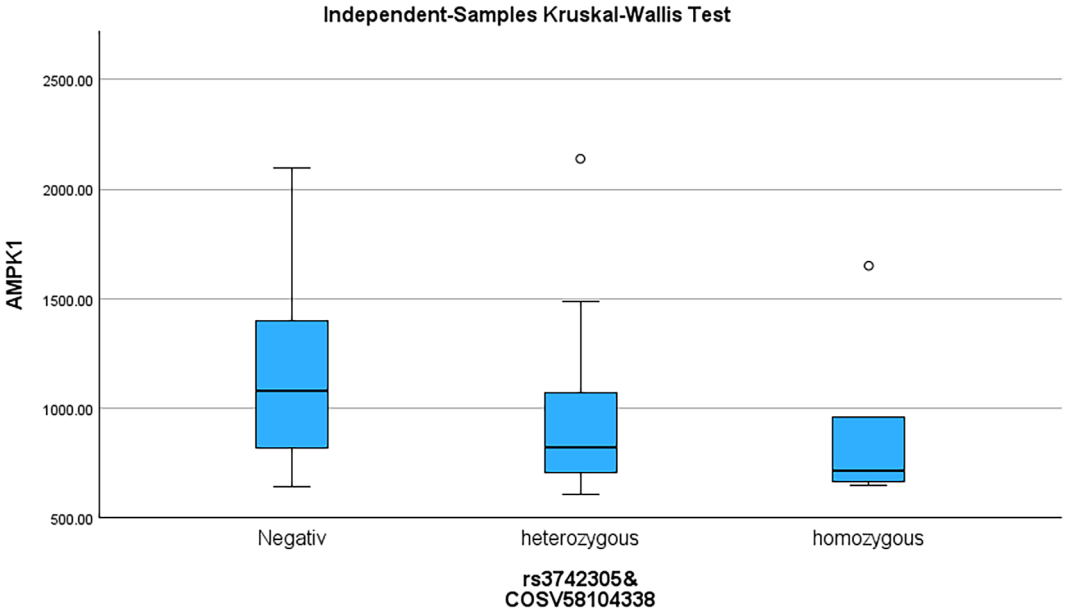

Figure 4. AMPK concentration based on SNV rs3742305andCOSV58104338 allele form.

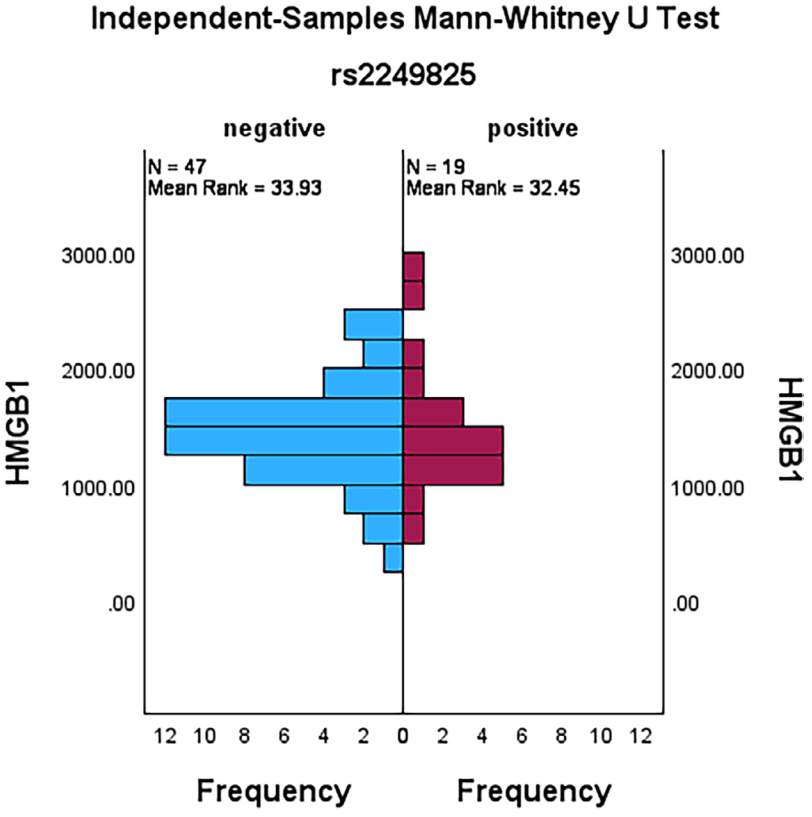

Figure 5. HMGB1concentration (pg/mL) based on SNV rs2249825 (+/–) status.

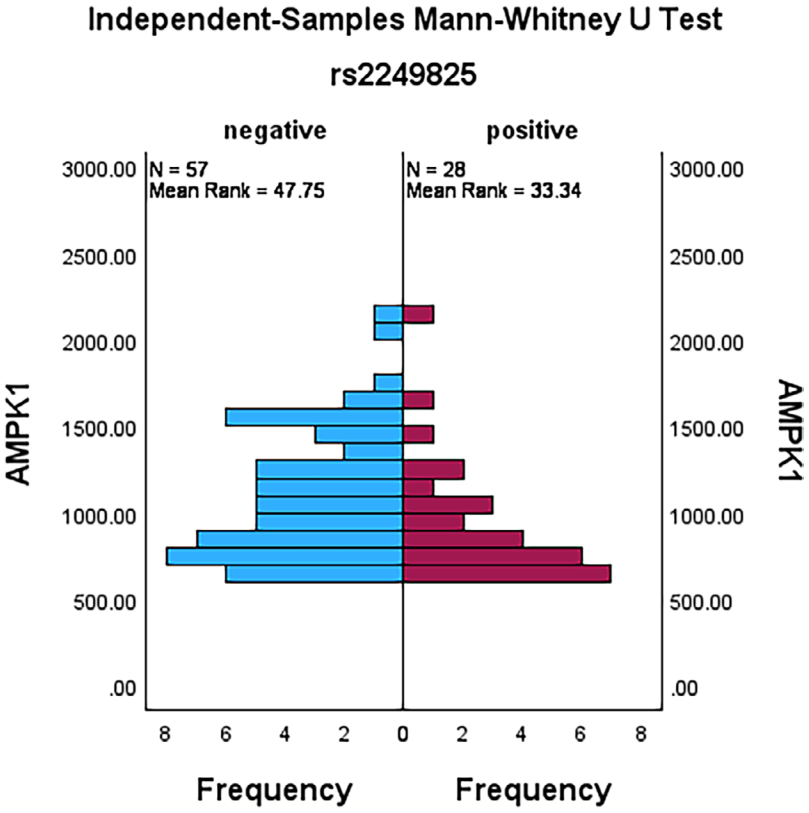

Figure 6. AMPK concentration (pg/mL) based on SNV rs2249825 (+/–) status.

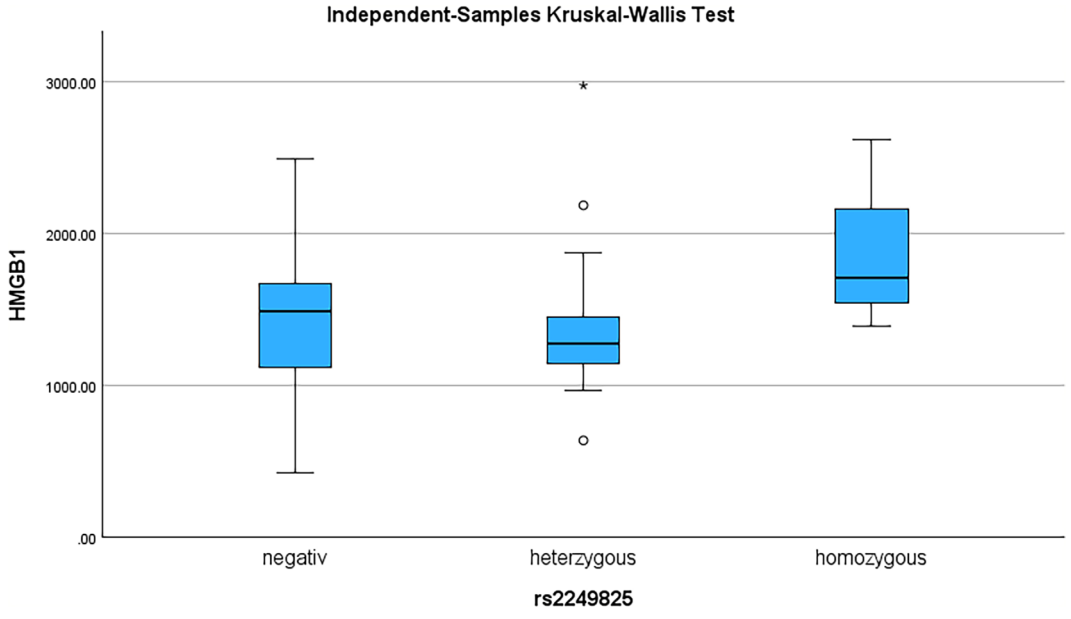

Figure 7. HMGB1 concentration based on SNV rs2249825 allele form.

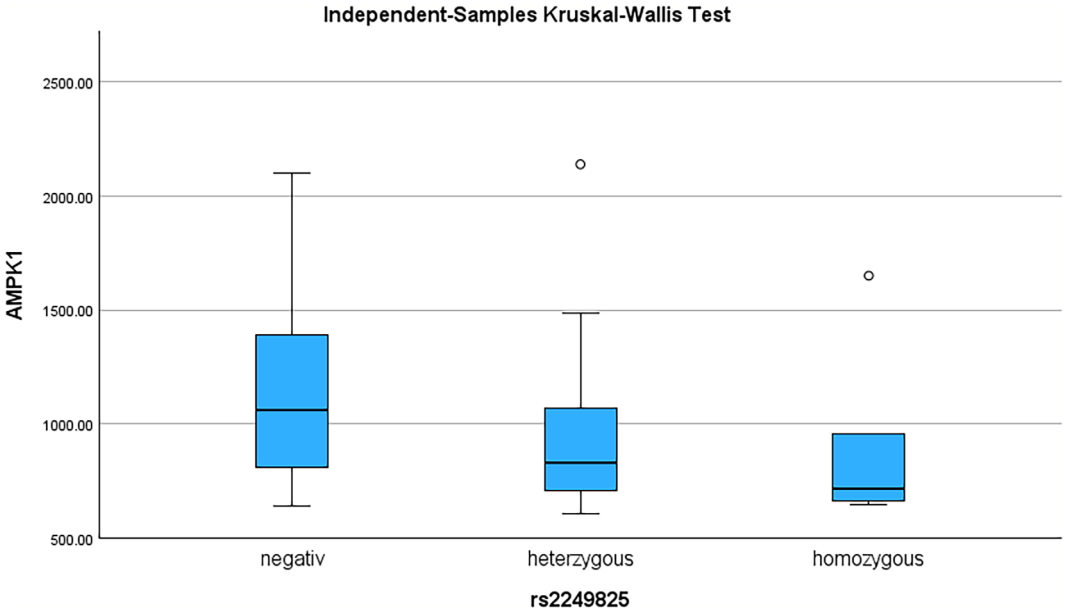

Figure 8. AMPK concentration based on the SNV rs2249825 allele form.

- Suggests this variant may be located in a non-functional intronic region or lacks regulatory influence on transcription or protein expression.

This SNP likely represents benign genetic variation without clinical or biomarker relevance in neonatal sepsis.

Cumulative Effect of Multiple SNPs

Newborns were grouped by total number of SNPs (1–4).

Key findings:

- AMPK levels declined systematically with increasing SNP count:
  - 1 SNP: Near-normal
  - 2–3 SNPs: Moderate decrease
  - 4 SNPs: Markedly reduced ($p < 0.05$) (Figure 9)
- HMGB1 showed a non-linear but upward trend, especially in 2–4 SNP groups.

Infants with 4 SNPs exhibited the lowest AMPK and highest HMGB1 (Figure 10), marking this group as potentially high-risk for severe metabolic collapse and excessive inflammation during sepsis.

These findings support a "gene load" effect, where the accumulated burden of functional SNPs magnifies clinical risk. To distinguish between disease-group effects and genotype-specific effects, we performed post-hoc stratified analyses. Within each clinical group (sepsis, pneumonia, control), the direction of genotype-related differences (higher HMGB1 and lower AMPK in variant carriers) remained consistent, although absolute biomarker levels differed between diseases. Two-way ANOVA (group × genotype) showed no significant interaction term ($p > 0.05$), indicating that genotype effects were additive rather than disease-specific. Thus, the statements "HMGB1 and AMPK are lower in sepsis vs pneumonia" refer to overall group means, whereas "elevated HMGB1 and reduced AMPK" describe within-group genotype associations.

Discussion

Genetic diversity and clinical outcomes in neonatal sepsis

This study highlights a critical, yet often overlooked, contributor to neonatal sepsis: host genetic makeup. While bacterial pathogens are the trigger,

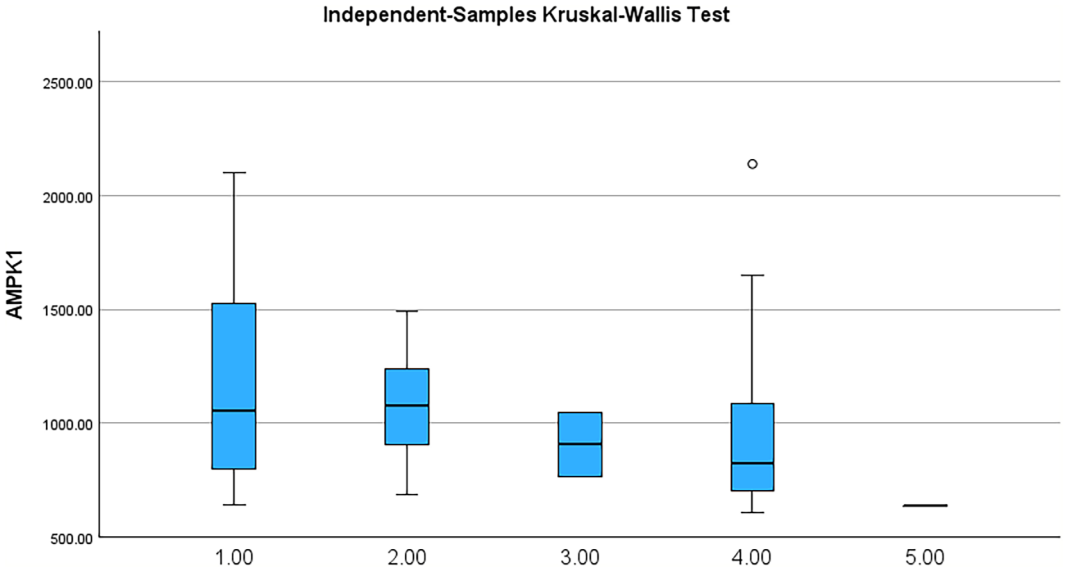

Figure 9. Comparison of AMPK levels by SNV count.

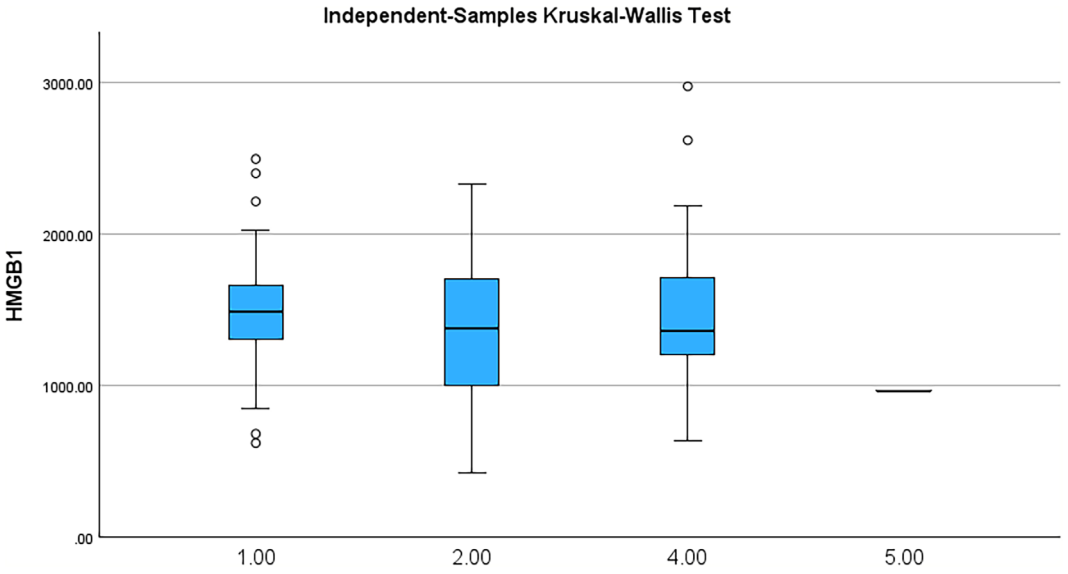

Figure 10. Comparison of HMGB1 levels by SNV count (1–4 variants).

the neonate's innate immune and metabolic responses, influenced by inherited polymorphisms, dictate how the disease progresses. Our findings demonstrate that SNPs in the HMGB1 gene are not merely silent genetic variants—they have functional consequences that significantly modulate inflammation (via HMGB1) and metabolic regulation (via AMPK). Infants with specific genotypes—especially homozygous forms of rs3742305 and rs2249825—showed significantly altered biomarker profiles, potentially predisposing them to more severe or treatment-resistant sepsis. Moreover, genetic stratification helps

explain why some newborns progress rapidly to septic shock despite early intervention, while others recover with minimal support. When interpreting these findings, it is important to separate two levels of effect: (1) disease-group differences, where mean HMGB1 and AMPK concentrations were globally lower in sepsis than in pneumonia, reflecting systemic consumption; and (2) genotype-related differences observed within each group, where carriers of functional HMGB1 variants consistently showed elevated HMGB1 and reduced AMPK relative to wild type. Interaction testing (group × genotype) did not reach statistical significance, suggesting that the genotype effect modulates baseline biomarker expression but does not differ significantly between disease states.

Interpretation of HMGB1 and AMPK alterations

HMGB1 is now widely recognised as a late inflammatory mediator, amplifying the cytokine storm. Its elevated levels in homozygous SNP carriers suggest enhanced transcriptional activity or post-transcriptional stability of HMGB1 mRNA/protein in these genotypes. Conversely, AMPK levels were significantly reduced in neonates with polymorphisms. This aligns with the hypothesis that genetic variants disrupt metabolic sensing, leading to poor cellular adaptation during stress. AMPK dysregulation not only weakens the immune system's endurance but also promotes organ dysfunction, a hallmark of advanced sepsis. Together, these dual biomarker trends—upregulated HMGB1 and downregulated AMPK—paint a picture of an over-inflamed yet energetically compromised host, especially in neonates with high SNP burden.

The Gene Load Hypothesis in Neonatal Sepsis

One of the most powerful takeaways from this study is the observed effect of cumulative SNP count:

- AMPK levels declined progressively with the number of SNPs.
- HMGB1 rose, though not always linearly, with higher SNP presence.

This "gene load" effect suggests that multiple functional SNPs can act synergistically, amplifying sepsis severity. It's a dose-dependent relationship, not merely the presence of a mutation, but the total burden that matters. This has profound implications for genetic screening and risk prediction.

These findings open new doors for precision medicine in neonatology. If SNP screening becomes accessible:

- Infants at genetic risk for poor outcomes can be closely monitored from birth.
- Aggressive or early treatments (e.g., anti-inflammatory agents, energy metabolism boosters) may be justified in high-risk genotypes.
- Serial HMGB1 and AMPK measurements could offer real-time insight into disease progression or treatment efficacy.

Such an approach would move neonatal sepsis care from a reactive, one-size-fits-all model to a proactive, personalised framework—potentially reducing morbidity and mortality.

Limitations and Future Directions

While our study provides novel insights, it has limitations:

- Sample size is modest (n = 99), warranting validation in larger cohorts.
- The study is single-center, and results may not generalize across populations or ethnic groups.
- Functional assays to confirm molecular mechanisms of SNP influence (e.g., transcription factor binding, mRNA stability) were not performed.

Future research should aim to:

- Explore ethnic variation in SNP prevalence and effect.
- Validate findings with functional genomics tools.
- Develop SNP-based scoring models to predict sepsis risk and guide therapy.
- Investigate targeted interventions that modulate AMPK or HMGB1 pathways based on genotype.

Conclusion

This study demonstrates that polymorphisms in the HMGB1 gene significantly influence both inflammatory and metabolic biomarkers (HMGB1 and AMPK) in neonates with sepsis. Key SNPs, including rs3742305, rs2249825, and rs41376448, were associated with elevated HMGB1 and suppressed AMPK, especially in homozygous or multi-SNP carriers. These changes correlate with increased sepsis risk and may offer predictive and therapeutic value. The concept of gene burden—the total number of functional SNPs—further enhances our understanding of sepsis heterogeneity. Incorporating genetic screening and biomarker profiling into NICU protocols could lead to personalised management strategies, enabling the early identification of high-risk neonates and tailoring interventions to improve outcomes.

Ethical Approval: All study procedures were reviewed and approved by the Ethics Committee of Azerbaijan Medical University (protocol No. 29, December 8, 2023). The protocol entitled *"The role of HMGB1 gene polymorphism and acute phase proteins in early diagnosis and prognosis of neonatal sepsis"* was considered compliant with bioethical standards, and the research was authorized for implementation.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

Authors' Contribution: PO Conceptualization, study design, data collection, laboratory analyses, interpretation of results, and drafting of the manuscript, NS Supervision of the research process, guidance in manuscript writing, and critical review of the final version, MO Statistical analysis, data visualization, and assistance with data interpretation, SG Methodology & Editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declaration on the Use of AI: None.

Consent for Publication: Written consent was obtained from the parents (father and mother) of the newborns. Information was provided regarding the research methods, the results obtained, and the use of the findings for scientific purposes.

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