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Dynamic changes of Systemic Immune-Inflammation Index during spontaneous term labor and its potential value as a predictive marker of postpartum hemorrhage

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Abstract

Objective: To characterize the dynamic changes of the systemic immune-inflammation index (SII) during spontaneous term labor to provide experimental support for the concept of a “systemic immune inflammation” process during labor, and to evaluate the predictive value of elevated SII during labor for postpartum hemorrhage (PPH).

Methods: This retrospective study encompassed deliveries from January 2022 to December 2025. A total of 622 women with uncomplicated, spontaneous full-term pregnancies who delivered vaginally were included. Peripheral venous blood samples were collected prior to labor and during labor for complete blood counts, from which SII was calculated as $(\text{neutrophils} \times \text{platelets}) / \text{lymphocytes}$. Dynamic changes in SII were analyzed. A case–control approach categorized participants into a PPH group (cases) and a non-PPH group (controls). SII levels before labor and during labor were compared between groups, and the predictive value of SII during labor for PPH was assessed using receiver operating characteristic (ROC) analysis.

Results: SII was significantly higher during spontaneous labor at term compared with the pre-labor baseline ($P < 0.001$). There were no significant differences in pre-labor SII between the PPH and non-PPH groups. However, SII during labor was markedly higher in the PPH group than in the non-PPH group ($P < 0.001$). ROC analysis yielded an area under the curve (AUC) of 0.7099 for SII during labor in predicting PPH, with the maximum Youden index of 0.358 corresponding to an SII cut-off of 1619.14. These

findings suggest that elevated SII during labor is associated with increased risk of PPH.

Conclusions : SII increases significantly during natural labor in otherwise uncomplicated pregnancies, supporting a potential role of systemic immune inflammation at labor onset. A high SII during labor may serve as a practical predictor of postpartum hemorrhage, offering a novel parameter for risk stratification and management.

Keywords : Systemic immune-inflammation index; postpartum hemorrhage; spontaneous term labor; natural parturition; predictive biomarker;

Background

Natural parturition is a complex, gradual physiological regulation process. The exact trigger mechanisms underlying labor initiation remain incompletely defined, and a single-cause explanation is unlikely. Consequently, the academic consensus supports a multifactorial model in which inflammatory responses serve as core drivers of labor initiation and progression. The systemic immune inflammation theory extends this concept by proposing that the remodeling of the maternal immune system at labor involves not only local changes at the maternal–fetal interface but also activation of systemic immune responses. Pregnancy represents maternal immune tolerance to the fetus, and the orderly activation of local and systemic inflammatory processes at term directly regulates the initiation and progression of labor, including the maintenance of uterine contractions and cervical changes [1]. The core signs of parturition are regular, progressively increasing uterine contractions (lasting ≥ 30 seconds each, with intervals of 5–6 minutes), accompanied by effacement and dilation of the cervix, fetal descent, and signs that cannot be suppressed by sedatives. According to the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Maternity and Neonatal Health (SMFM), term pregnancy is subdivided into early term (37-38+6/7 weeks), full term (39-40+6/7 weeks), and late term (41-41+6/7 weeks); gestational age ≥ 42 weeks is classified as post-term. This study focuses on the natural labor experiences of healthy, full-term pregnancies to explore inflammation-related changes.

Systemic immune inflammation index (SII) is a relatively novel inflammatory index initially used to assess prognosis in malignancies and inflammatory diseases. In recent years, SII has demonstrated advantages in monitoring systemic inflammatory responses. SII, calculated from peripheral blood counts (neutrophils N, platelets P, lymphocytes L) as $SII = (N \times P) / L$, integrates multiple hematopoietic lineages and may better reflect the overall systemic immune inflammatory status than single biomarkers, with less susceptibility to individual hematopoietic variation [2-4]. Given that complete blood count is a routine, inexpensive, and reproducible test, SII offers feasibility for large-scale dynamic monitoring in clinical settings [5]. Based on the systemic immune inflammation theory of labor initiation, we hypothesize that the dynamic changes in SII before and after natural term labor may provide new experimental evidence for this theory and offer a convenient framework for investigating the inflammatory mechanisms underlying labor initiation.

Postpartum hemorrhage (PPH) is a major obstetric emergency, defined as vaginal-delivery blood loss ≥ 500 mL, cesarean-delivery blood loss ≥ 1000 mL, or hypovolemia signs and symptoms within 24 hours after delivery. PPH remains a leading cause of maternal morbidity and mortality worldwide, accounting for a substantial proportion of obstetric deaths despite advances in care [6-10]. Emerging evidence suggests that placental inflammatory factors can disrupt villous cellular integrity and function, contributing to obstetric complications and driving a shift toward etiologically targeted interventions rather than purely conservative management. Inflammatory regulation has thus emerged as a new therapeutic entry point for preventing and managing related complications [11-17].

Patients and methods

Study participants

This is a retrospective study conducted at Gutian County Hospital and approved by the Ethics Committee of Gutian County Hospital. Eligible participants were pregnant women who attended routine prenatal care at our hospital and delivered between January 2022 and December 2025. Given that the study used anonymized medical records, informed consent was waived.

Inclusion criteria

1. age ≥ 18 years;

- 2.natural (spontaneous) parturition between 37 and 42 weeks of gestation;
- 3.complete and accessible clinical and laboratory data required for this study.

Exclusion criteria

- 1.pregnancy complications, including gestational diabetes mellitus, hypertensive disorders of pregnancy, intrahepatic cholestasis of pregnancy, etc.
- 2.fetal/neonatal factors such as post-embryo transfer pregnancies, multiple pregnancy, preterm birth, etc.
- 3.non-spontaneous labor: premature rupture of membranes or labor induction requiring
- 4.pharmacologic or mechanical methods;
- 5.cesarean delivery.

Statistical methods

SPSS 31.0 statistical software was used for data analysis, and the data normality was evaluated by Kolmogorov Smirnov test. Non parametric Mann Whitney U test was used to compare the differences between two groups, and Kruskal Wallis h test was used to compare the differences between multiple groups. The measurement data were expressed as median and interquartile range. In this study, extreme outliers were eliminated according to the Tukey rule in CLSI c28-a326, and graph pad prism 10.0 software was used to draw relevant graphs.

Data quality control

A rigorous data quality framework was implemented. All personnel involved in data handling underwent uniform training. Data collection, collation, and entry were conducted by a designated, trained staff member. Throughout the study, blinded procedures were employed to reduce bias and enhance data reliability. Regular quality checks and audits were performed to ensure data integrity and traceability.

Data collection

Baseline demographic data were extracted from the hospital medical records information management system, including age, parity, and gestational age at delivery. Concurrently, clinical information such as pregnancy complications, mode of delivery, and postpartum hemorrhage was collected.

Sample collection

Blood samples were analyzed using the Sysmex xn-2800 hematology analyzer (Sysmex, Japan). For each subject, 2 mL of peripheral venous blood was collected, and hematologic assessment was conducted using flow cytometry-based fluorescence staining. Details of gestational age and labor status at the time of sampling (pre-delivery vs during delivery) were recorded.

Hematological analysis

From the peripheral blood routine results, neutrophil count (n), platelet count (P), and lymphocyte count (L) were extracted. The Systemic Immune Inflammation Index (SII) was calculated as:

$$SII = \frac{P \times n}{L}$$

where P is platelet count, n is neutrophil count, and L is lymphocyte count.

Statistical methods

Analyses were performed with SPSS Statistics 31.0. Normality of data was assessed using the Kolmogorov–Smirnov test. Categorical variables are presented as counts and percentages. Continuous variables are reported as medians with interquartile ranges (IQR) or 2.5th–97.5th percentiles, as appropriate. Extreme outliers were excluded according to the Tukey rule in accordance with CLSI guidelines (CLSI c28-a326). Graphical data representations were generated with GraphPad Prism 10.0. Statistical significance was set at $P < 0.05$.

Results

Participants' characteristics

A total of 622 cases of pregnant women who underwent routine prenatal examinations and delivered vaginally at term were retrospectively collected from Gutian County Hospital between January 2022 and December 2025. Exclusion criteria ensured absence of pregnancy complications and any obstetric interventions that could confound inflammatory markers. The cohort characteristics were as follows: maternal age median 27 years (interquartile range [IQR] 29-32), parity 2 (IQR 2-3), number of births 1 (IQR 1-2), and gestational age at delivery 39 weeks (IQR 38-39). Baseline blood routine indices and the systemic immune inflammation index (SII) were derived

from peripheral blood samples collected before and at the time of delivery. SII was calculated as $SII = P \times N / L$, where P is platelet count, N is neutrophil count, and L is lymphocyte count.

Changes of SII in term, uncomplicated pregnancies during labor

In women with term, uncomplicated pregnancies, the SII level during labor was significantly higher than that before labor. The observed increase was statistically significant ($P < 0.001$). These results are summarized in Table 1 and illustrated in Figure 1.

Table 1. Changes in the SII in term, uncomplicated pregnancies during labor

Variables	SII before labor	SII during labor	Z	P
N=622	742.60 (592.44, 974.19)	924.30 (654.28, 1303.53)	-10.08	<0.001

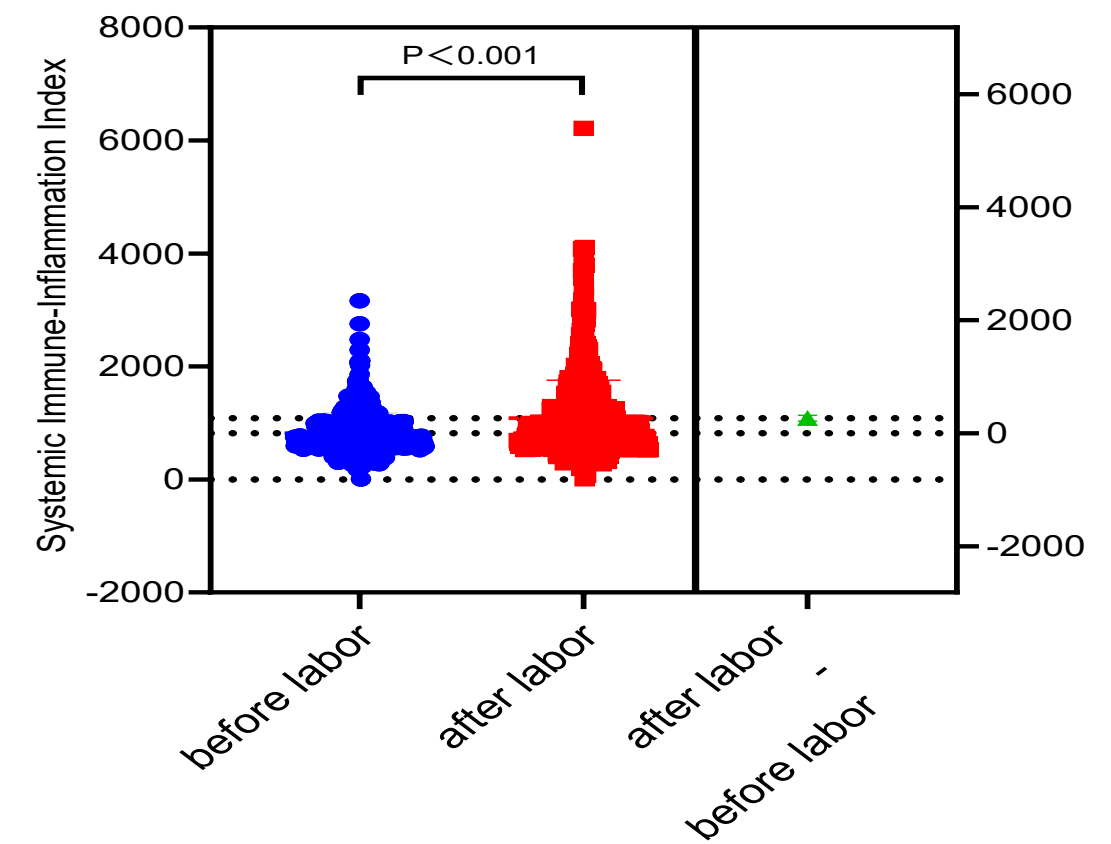


Figure 1. Changes in the SII in term, uncomplicated pregnancies during labor

Changes of Systemic Immune Inflammation Index (SII) in parturients with postpartum hemorrhage

A total of 622 pregnant women were analyzed, including 604 in the non-postpartum hemorrhage (non-PPH) group and 18 in the postpartum hemorrhage (PPH) group. There was no significant difference in SII between groups before delivery ($P > 0.05$). During labor, SII was significantly higher in the PPH group than in the non-PPH group ($P < 0.05$). These findings are summarized in Table 2 and illustrated in Figure 2.

Table 2. Changes of SII in parturient women with postpartum hemorrhage

Variables	control group (N=604)	Case group (N=18)	Z	P
Age	30.00 (27.00, 32.25)	30.00 (27.00, 32.00)	-0.764	> 0.05
Number of pregnancies	2.00 (1.75, 3.00)	2.00 (2.00, 3.00)	-0.04	> 0.05
Parity	1.00 (0.75, 2.00)	1.00 (1.00, 2.00)	-0.69	> 0.05
Gestational age at delivery	39.0 (37.75, 39.00)	39.00 (38.00, 39.00)	-1.401	> 0.05
SII before labor	739.03 (591.46, 974.61)	819.73 (576.48, 939.84)	-1.52	> 0.05
SII during labor	916.15 (650.22, 1286.3)	1524.30 (815.66, 2488.58)	-2.025	< 0.05

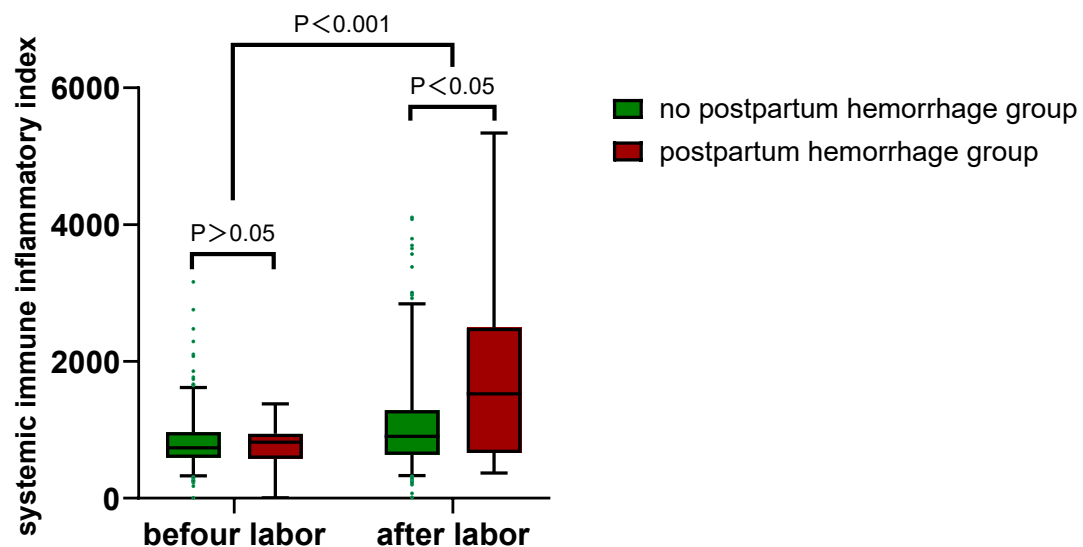


Figure 2 . Changes of SII in parturient women with postpartum hemorrhage

Diagnostic performance of SII

Receiver operating characteristic (ROC) curve analysis was conducted to assess the ability of SII to distinguish PPH. The area under the curve (AUC) was 0.710 (95% CI not provided in original text; please insert if available). The maximum Youden index was 0.358, corresponding to an optimal SII cutoff of 1619.14. Sensitivity and specificity at this cutoff should be reported if available. These findings are illustrated in Figure 3.

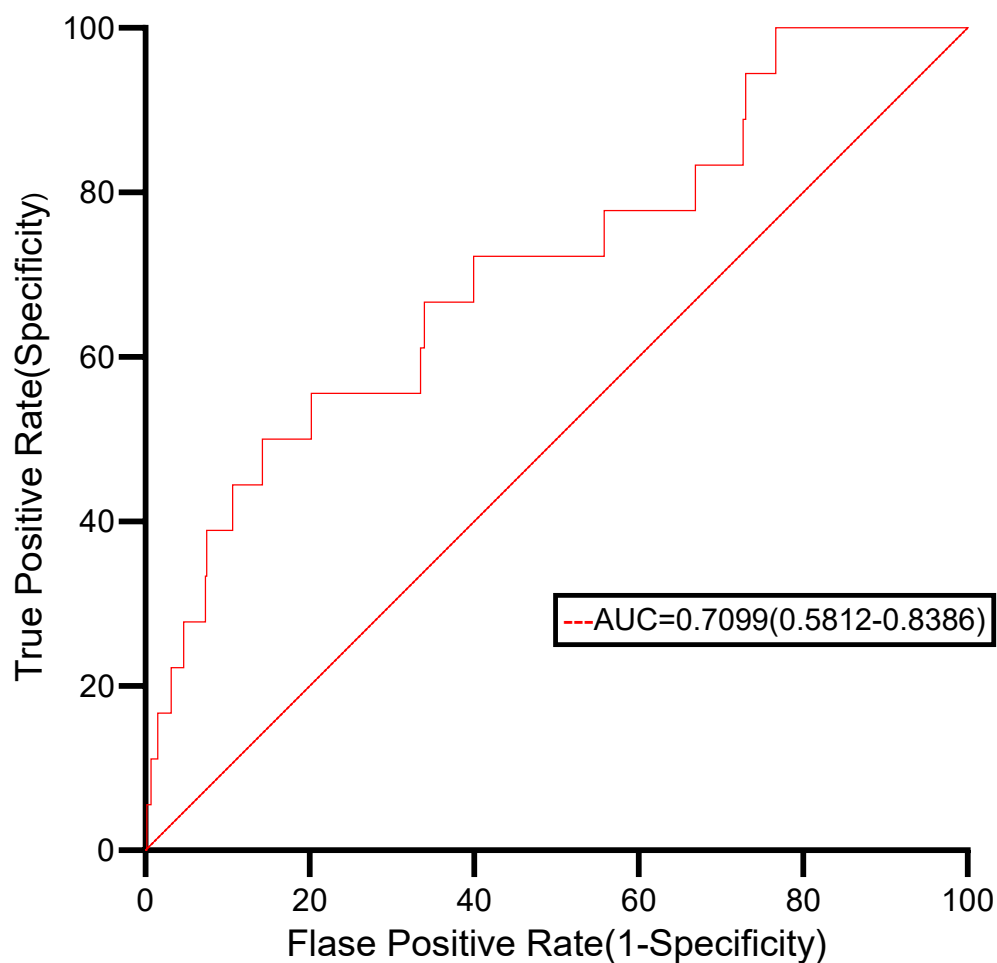


Figure 3 . ROC Curves of Single Indicators for Postpartum hemorrhage

Discussion

The Systemic Immune-Inflammation Index (SII) was first proposed by Hu et al. in 2014

and integrates three readily available hematologic parameters: platelet count (P), neutrophil count (N), and lymphocyte count (L). Calculated as $SII = P \times N / L$, the index reflects the balance between pro-inflammatory mediators (neutrophils and platelets) and regulatory lymphocytes, thereby serving as a composite marker of systemic inflammation and immune status. Since its introduction, SII has been increasingly adopted as a prognostic tool across a wide spectrum of diseases, particularly malignancies such as cholangiocarcinoma, thyroid cancer, melanoma, bladder cancer, glioblastoma, oral squamous cell carcinoma, lymphoma, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, renal cell carcinoma, nasopharyngeal carcinoma, esophageal cancer, ovarian/peritoneal cancer, small cell lung cancer, and cervical cancer. Beyond oncology, SII has been explored in inflammatory and autoimmune conditions (including myocarditis, pancreatitis, psoriatic arthritis, necrotizing enterocolitis, ankylosing spondylitis, Behçet's disease, acne, acute pyelonephritis, and systemic lupus erythematosus) and in infectious and cardiovascular diseases. Notably, recent research indicates that elevated SII may predict adverse outcomes in COVID-19 and cardiovascular events such as acute coronary syndrome, myocardial infarction, and stroke, as well as adverse obstetric outcomes including abortion, missed abortion, and premature rupture of membranes[18-49]. Collectively, these findings support the utility of SII as a versatile, cost-effective biomarker for assessing inflammatory status and prognostic risk across diverse clinical contexts, including pregnancy and obstetric complications. Future work should aim to establish standardized cutoffs, account for confounding factors (e.g., infection, medication, gestational age), and validate SII in prospective obstetric cohorts to enhance its translational value in maternal-fetal medicine.

Natural parturition is a tightly regulated physiological inflammatory process in which uterine contraction, cervical maturation, chorioamniotic membrane activation, and systemic inflammatory responses intertwine to initiate and progress labor. Cytokines and mediators such as prostaglandins, IL-1 β , IL-6, and TNF- α drive these processes, with transcriptomic and immunologic studies revealing distinct immunological signatures in peripheral blood that reflect delivery status and may identify risk for adverse obstetric outcomes [50]. Immune cells at the maternal–fetal interface (neutrophils, macrophages, NK cells, etc.) and their cytokines regulate labor, and decidual immune-cell imbalances or premature activation of inflammatory pathways are linked to preterm delivery [51]. IL-6 has been highlighted as a core mediator of labor, promoting uterine contractions, fetal membrane activation, and

cervical maturation, while TNF signaling and NLR pathways contribute to labor-associated tissue remodeling and inflammatory signaling [52]. Other studies have focused on immune signals and interventions and species-specific inflammatory responses[53-59]. Across species, changes in immune cell composition and inflammatory state during the perinatal period reinforce the connection between delivery and inflammation and suggest that peripheral inflammatory signals can serve as accessible biomarkers of parturition status [60-61]. Collectively, these findings support a model in which inflammatory mediators drive labor via NF- κ B and AP-1-dependent pathways, with complement activation further amplifying inflammatory cascades to facilitate labor [21-23, 62-66]. The balance between proinflammatory (N1) and regulatory (N2) neutrophil phenotypes, modulated by cytokines such as IL-10, appears critical for normal delivery; dysregulation (e.g., sustained N1 activation) may predispose to premature delivery or obstetric complications [67]. Monocyte/macrophage-derived mediators (e.g., TNF- α) participate in cervical softening and contraction onset, yet excessive activation may trigger fetal inflammatory responses, including FIRS [68-69]. Tissue-specific dynamics-from choriodecidual to myometrial sites-further shape labor timing, and while inflammation may act as a trigger, a bidirectional relationship with hormonal signaling (e.g., progesterone receptor pathways) likely exists [66, 69-73]. Given these mechanisms, peripheral inflammatory markers offer a noninvasive window into the intrauterine milieu and labor status, with combined panels of cytokines and complement components potentially outperforming single markers in predicting term delivery [74-77]. The present study adds to this framework by demonstrating that the systemic immune inflammation index (SII) rises in healthy term parturients, supporting its utility as a simple, integrative marker of labor-associated inflammation.

Postpartum hemorrhage (PPH) remains a major obstetric risk, with uterine atony as its primary cause. Inflammation is a central driver of uterine contractile dysfunction, and systemic immune-inflammation markers such as the systemic immune inflammatory index (SII) and circulating pro-inflammatory cytokines have been associated with PPH. Emrullah Akay and colleagues reported that SII serves as an important predictor of PPH risk, identifying a cut-off around 915. However, this study faced limitations, including sample bias, unclear detection timing, potential confounders, and an unclear mechanistic link between SII and PPH etiology [78]. The concept of postpartum acute myositis (PAM) proposed by Tomoaki Oda et al. suggests inflammation impairs myometrial contractility via immune cell infiltration [79], a notion that, when viewed alongside SII, raises the possibility that excessive

inflammatory activation reflected by high SII may contribute to PAM and subsequent contractile asthenia in PPH. Additional evidence indicates elevated plasma IL-16, IL-6, and other pro-inflammatory cytokines in PPH patients prior to delivery, highlighting potential biomarkers and therapeutic targets [80]. Multi-omics analyses reveal a pro-inflammatory uterine microenvironment in atonic PPH, implicating immune pathways and mediators (e.g., IL-6, TNF- α) and immune cells (neutrophils, macrophages) in the pathogenesis by enhancing inflammation and impairing myometrial function [81-82]. Clinical data also show higher maternal plasma inflammatory markers in PPH, which may disrupt myometrial contractility and promote blood loss; case-control studies have demonstrated elevated cytokine levels in PPH versus controls [83-84]. While these findings support a mechanistic link between inflammation and uterine atony, the evidence remains largely observational, and prospective, mechanistic validation is needed. Comprehensive cytokine profiling (e.g., assessment of up to ~48 cytokines) has identified associations between specific inflammatory factors and PPH risk, underscoring the potential for inflammation-informed predictive models [85-86]. In summary, accumulated evidence supports inflammation as a fundamental pathological basis of PPH via activation of immune pathways, amplification of pro-inflammatory mediators, and impairment of myometrial contractility, but robust translational validation is required before routine clinical application.

In summary, while accumulating evidence supports a mechanistic link between systemic inflammation, SII elevation, and obstetric complications such as PPH due to uterine atony, several limitations temper the translational impact of current findings. Many studies are observational or retrospective, with heterogeneous populations, small sample sizes, and potential confounders (infection, medications, gestational age) that are not adequately controlled. The timing of biomarker assessment often remains undefined, hindering causal inferences and the establishment of clinically actionable cutoffs. Mechanistic pathways linking SII components to myometrial contractility require rigorous prospective validation, including longitudinal sampling across the perinatal period and multi-omics integration to map causal networks. Future research should standardize SII measurement and cutoff strategies, validate predictive models in diverse, prospective obstetric cohorts, and delineate the temporal-spatial regulatory mechanisms by which inflammation interfaces with progesterone signaling and myometrial function to inform targeted prevention and therapeutic strategies.

Conclusions

SII increases significantly during natural labor in otherwise uncomplicated pregnancies, supporting a potential role of systemic immune inflammation at labor onset. A high SII during labor may serve as a practical predictor of postpartum hemorrhage, offering a novel parameter for risk stratification and management. While these findings are promising, standardized SII cutoffs in pregnancy, consideration of gestational age and comorbid conditions, and prospective validation in diverse cohorts are needed before routine clinical adoption. Future work should delineate temporal dynamics of SII across the perinatal period, explore mechanistic links among SII components (platelets, neutrophils, lymphocytes), and assess how SII interacts with established obstetric risk factors and interventions. Together, these efforts will clarify the role of systemic inflammation in labor biology and determine whether SII can inform risk stratification and management during delivery.

List of abbreviations

SII: systemic immune-inflammation index

PPH: postpartum hemorrhage

ROC: receiver operating characteristic

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Gutian County Hospital, China (approval no MECGTCH 2025-010801).

Consent for publication

Written informed consent was obtained from the patient for the publication of their anonymized medical information.

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions. Data may be requested from the

corresponding author with approval from the relevant ethics committee.

Competing interests

The authors declare that there is no conflict of interest.

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Author ' contributions

WZ and YFL designed the study and participated in data collection. WZ performed the systematic review and drafted the manuscript. HFL edited and reviewed the manuscript. YLB, LZH, WYZ, and YFL contributed to the conception of the study. All authors contributed to the article and approved the submitted version.

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References

1. Chan YTV, Lau KW, Hui W, et al. Measurement of cervical length and head perineum distance before labor to predict time of delivery. *J Matern Fetal Neonatal Med.* 2022;35(25):4905-4909.
2. van Gerwen M, Cooke PV, Alpert N, et al. Patient-reported outcomes following total thyroidectomy and lobectomy in thyroid cancer survivors: an analysis of the PROFILES Registry data. *Support Care Cancer.* 2022;30:687-693.
3. Yang R, Chang Q, Meng X, et al. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. *J Cancer.* 2018;9:3295-3302.
4. Li M, Li Z, Wang Z, et al. Prognostic value of systemic immune-inflammation index in patients with pancreatic cancer: a meta-analysis. *Clin Exp Med.* 2022. doi:10.1007/s1023802100785x.
5. Li C, Tian W, Zhao F, et al. Systemic immune inflammation index, SII, for prognosis of elderly patients with newly diagnosed tumors. *Onco.*
6. Gong J, Chen Z, Zhang Y, et al. Risk-factor model for postpartum hemorrhage after cesarean delivery: a retrospective study based on 3498 patients. *Sci Rep.* 2022;12:22100.

7. Rakesh G, Olorunfemi O, Nicole S, et al. Heat stable carbetocin or oxytocin for prevention of postpartum hemorrhage among women at risk: A secondary analysis of the CHAMPION trial. *Int J Gynaecol Obstet.* 2024;164(1):1.
8. Wei J, Dai Y, Wang Z, et al. Intrauterine double-balloon tamponade vs gauze packing in the management of placenta previa: a multicentre randomized controlled trial. *Medicine (Baltim).* 2020;99:e19221.
9. World Health Organization, UNICEF. [Document title not provided]. 2019. Accessed 1 Jun 2023. <https://www.who.int/publications/i/item/97892415>.
10. Zhou C, Zhang L, Bao Y, et al. Effect of blood transfusion during cesarean section on postpartum hemorrhage in a tertiary hospital over a 4-year period. *Medicine (Baltim).* 2021;100:e23885.
11. Tanacan A, Uyanik E, Unal C, et al. A cut-off value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. *J Obstet Gynaecol Res.* 2020;46(8):1333-1341.
12. Erdem A, Erdem M, Sahila S, et al. Predicting Gestational Diabetes Mellitus Using The Systemic Immune-Inflammation Index in The First Trimester. *J Contemp Med.* 2022;12(5):617-620.
13. Sahin R, Tanacan A, Serbetci H, et al. The role of first-trimester NLR (neutrophil to lymphocyte ratio), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI) in the prediction of composite adverse outcomes in pregnant women with systemic lupus erythematosus. *J Reprod Immunol.* 2023;158:103978.
14. Sahin R, Tanacan A, Serbetci H, et al. First-trimester neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI) as predictors of composite adverse outcomes in pregnant women with Familial Mediterranean fever. *Z Geburtshilfe Neonatol.* 2023. 973.
15. Tanacan A, Uyanik E, Unal C, et al. A cut-off value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. *J Obstet Gynaecol Res.* 2020;46(8):1333-1341.
16. Bai YY, Xi Y, Yin BB, et al. Reference intervals of systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio during normal pregnancy in China. *Eur Rev Med Pharmacol Sci.* 2023;27(3):1033-1044.
17. Gallo DM, Romero R, Bosco M, et al. Maternal plasma cytokines and the subsequent risk of uterine atony and postpartum hemorrhage. *J Perinat Med.* 2023;51(2):219-232.
18. Liu D, Huang XY, Xu ZX, et al. Predictive value of nlr and plr in missed miscarriage. *J Clin Lab Anal.* 2022;36:e24250.
19. Liu XC, Jiang YP, Sun XG, et al. Prognostic Significance of the Systemic Immune-Inflammation Index in Patients With Cholangiocarcinoma: A Meta-Analysis. *Front Oncol.* 2022;12:938549.
20. Kars A, Sahin A, K yl c K, et al. Systemic immune inflammation index in differentiated thyroid cancers. *Acta Otorhinolaryngol Ital.* 2022;42(2):150-154.

21. Susok L, Said S, Reinert D, et al. The pan-immune-inflammation value and systemic immune-inflammation index in advanced melanoma patients under immunotherapy. *J Cancer Res Clin Oncol*. 2022;148(11):3103-3108.
22. Li J, Cao DH, Huang Y, et al. The Prognostic and Clinicopathological Significance of Systemic Immune-Inflammation Index in Bladder Cancer. *Front Immunol*. 2022;13:865643.
23. Hung MY, Xu CAP, Coutu BG, et al. The Prognostic Significance of Systemic Immune-Inflammation Index in Patients With Glioblastoma. *Int J Radiat Oncol Biol Phys*. 2021;111(3):e591.
24. Kubota K, Ito R, Narita N, et al. Utility of prognostic nutritional index and systemic immune-inflammation index in oral cancer treatment. *BMC Cancer*. 2022;22(1):368.
25. Wu J, Zhu H, Zhang Q, et al. Nomogram based on the systemic immune-inflammation index for predicting the prognosis of diffuse large B-cell lymphoma. *Asia Pac J Clin Oncol*. 2023;19(2):e138-e148.
26. Li J, Shao JJ, Zhang XL, et al. Prognostic Value of the Pretreatment Systemic Immune-Inflammation Index in Patients with Colorectal Cancer. *Gastroenterol Res Pract*. 2020;2020:8781674.
27. Zhao M, Duan XL, Han X, et al. Sarcopenia and Systemic Inflammation Response Index Predict Response to Systemic Therapy for Hepatocellular Carcinoma and Are Associated With Immune Cells. *Front Oncol*. 2022;12:854096.
28. Han RS, Tian ZB, Jiang YP, et al. Prognostic significance of the systemic immune inflammation index in patients with metastatic and unresectable pancreatic cancer. *Front Surg*. 2022;9:915599.
29. Stühler V, Herrmann L, Rausch S, et al. Role of the Systemic Immune-Inflammation Index in Patients with Metastatic Renal Cell Carcinoma Treated with First-Line Ipilimumab plus Nivolumab. *Cancers (Basel)*. 2022;14(12):2972.
30. Zeng ZS, Xu SG, Wang DT, et al. Prognostic significance of systemic immune-inflammation index in patients with nasopharyngeal carcinoma: a meta-analysis. *Syst Rev*. 2022;11(1):247.
31. Li XQ, Zhang SH, Lu J, et al. The prognostic value of systemic immune-inflammation index in surgical esophageal cancer patients: An updated meta-analysis. *Front Surg*. 2022;9:922595.
32. Ramón-Rodríguez J, De-Armas-Conde N, Jaén-Torrejimeno I, et al. Prognostic value of pre-operative systemic immune-inflammation index and platelet to lymphocyte ratio in peritoneal carcinomatosis of ovarian origin. *Surg Oncol*. 2022;42:101750. doi:10.1016/j.suronc.2022.101750.
33. Zhou YT, Dai ML, Zhang ZX. Prognostic Significance of the Systemic Immune-Inflammation Index (SII) in Patients With Small Cell Lung Cancer: A Meta-Analysis. *Front Oncol*. 2022;12:814727.
34. Liu PP, Jiang YN, Zheng XJ, et al. Pretreatment Systemic Immune-Inflammation Index Can Predict Response to Neoadjuvant Chemotherapy in Cervical Cancer at Stages IB2-IIB. *Pathol Oncol Res*. 2022;28:1610294.
35. Huang HP, Liu Q, Zhu LX, et al. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical Cancer. *Sci Rep*. 2019;9(1):3284.
36. Yaradilmiş RM, Güneylüoğlu MM, Öztürk B, et al. A Novel Marker for Predicting Fulminant Myocarditis: Systemic Immune-Inflammation Index. *Pediatr Cardiol*. 2023;44(3):647-655.

37. Biyik M, Biyik Z, Asil M, et al. Systemic Inflammation Response Index and Systemic Immune Inflammation Index Are Associated with Clinical Outcomes in Patients with Acute Pancreatitis? *J Invest Surg.* 2022;35(8):1613-1620.
38. Atalay F, Kars A, Topal K, et al. Systemic immune inflammation index in patients with recurrent aphthous stomatitis. *Braz J Otorhinolaryngol.* 2022;88(4):621-624. doi:10.1016/j.bjorl.2022.02.007.
39. Kelesoglu Dincer AB, Sezer S. Systemic Immune Inflammation Index as a Reliable Disease Activity Marker in Psoriatic Arthritis. *J Coll Physicians Surg Pak.* 2022;32(6):773-778.
40. Feng W, Hou JP, Xiang CZ, et al. Correlation of systemic immune-inflammation Index with surgical necrotizing enterocolitis. *Front Pediatr.* 2022;10:1044449. doi:10.3389/fped.2022.1044449.
41. Wu JL, Yan LF, Chai KX. Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. *J Clin Lab Anal.* 2021;35(9):e23964.
42. Tanacan E, Dincer D, Erdogan FG, et al. A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease. *Clin Exp Dermatol.* 2021;46(2):286-291.
43. Cosansu NC, Yuksekal G, Turan U, et al. Investigation of systemic immune-inflammation index and systemic inflammation response index as an indicator of the anti-inflammatuary effect of isotretinoin in patients with acne vulgaris. *Cutan Ocul Toxicol.* 2022;41(2):174-178.
44. Karakaya D, Güngör T, Cakýcý EK, et al. Determining the effectiveness of the immature granulocyte percentage and systemic immune-inflammation index in predicting acute pyelonephritis. *Postgrad Med.* 2023;135(2):155-160.
45. Ozdemir A, Baran E, Kutu M, et al. Could systemic immune inflammation index be a new parameter for diagnosis and disease activity assessment in systemic lupus erythematosus? *Int Urol Nephrol.* 2023;55(1):211-216.
46. Karaaslan T, Karaaslan E. Predictive Value of Systemic Immune-inflammation Index in Determining Mortality in COVID-19 Patients. *J Crit Care Med (Targu Mures).* 2022;8(3):156-164.
47. Adali MK, Buber I, Kilic O, et al. Ticagrelor improves systemic immune-inflammation index in acute coronary syndrome patients. *Acta Cardiol.* 2022;77(7):632-638.
48. Dolu AK, Karayiđit O, Ozkan C, et al. Relationship between intracoronary thrombus burden and systemic immune-inflammation index in patients with ST-segment elevation myocardial infarction. *Acta Cardiol.* 2023;78(1):72-79.
49. Zhou YX, Li WC, Xia SH, et al. Predictive Value of the Systemic Immune Inflammation Index for Adverse Outcomes in Patients With Acute Ischemic Stroke. *Front Neurol.* 2022;13:836595.
50. Gomez-Lopez N, Romero R, Galaz J, et al. Transcriptome changes in maternal peripheral blood during term parturition mimic perturbations preceding spontaneous preterm birth. *Biol Reprod.* 2022;106(1):185-199.
51. Lv M, Jia YH, Dong JQ, et al. The landscape of decidual immune cells at the maternal-fetal interface in parturition and preterm birth. *Inflamm Res.* 2025;74(1):44.
52. Ding WJ, Chim SSC, Wang CC, et al. Molecular Mechanism and Pathways of Normal Human Parturition in Different Gestational Tissues: A Systematic Review of Transcriptome Studies. *Front Physiol.* 2021;12:730030.

53. Ando K, Hédou JJ, Feyaerts D, et al. A Peripheral Immune Signature of Labor Induction. *Front Immunol.* 2021;12:725989.
54. Areia AL, Moura P, Mota-Pinto A. The role of innate immunity in spontaneous preterm labor: A systematic review. *J Reprod Immunol.* 2019;136:102616.
55. Obeagu EI. Monocytes and parturition: Linking prolonged labor to immune dysregulation. *Medicine.* 2025;104(17):e42351.
56. Reznik SE, Kashou A, Ward D, et al. N,N-dimethylacetamide blocks inflammation-induced preterm birth and remediates maternal systemic immune responses. *Sci Rep.* 2025;15(1):8234.
57. Chen ZX, Shan YL, You XJ, et al. NLRP3 inflammasome is involved in uterine activation for labor at term and preterm. *Reproduction.* 2021;162(6):449-460.
58. Gray JM, Castillo-Ruiz A, Major KM, et al. The inflammatory response to birth requires MyD88 and is driven by both mother and offspring. *Brain Behav Immun.* 2024;115:617-630.
59. Siewiera o, McIntyre TI, Cautivo KM, et al. Circumvention of luteolysis reveals parturition pathways in mice dependent upon innate type 2 immunity. *Immunity.* 2023;56(3):606.
60. Hussien J, al-Mubarak AIA, Al-Humam NA. Changes in immune cell composition during the periparturient period in female dromedary camels. *Pak Vet J.* 2021;41(2):221-227.
61. Fang H, Zhao YL, Akonyani ZP, et al. Rectal Microbiomes and Serum Metabolomics Reveal Changes in Serum Antioxidant Status and Immune Responses of Dezhou Donkeys in Late Gestation to Parturition. *Antioxidants (Basel).* 2025;14(10):1253.
62. Huang Q, Li P, Zheng Z, et al. The synergistic effects of prostaglandin and IL-1 β on myometrial and cervical stromal cells at the onset of labor. *Cytokine.* 2025;190:156927.
63. Chen CL, Zhu SY, Bai L, et al. The Role of Formyl Peptide Receptor 1 in Uterine Contraction During Parturition. *Front Pharmacol.* 2021;12:696697.
64. Singh N, Herbert B, Sooranna GR, et al. Is myometrial inflammation a cause or a consequence of term human labour? *J Endocrinol.* 2017;235(1):69-83.
65. Talati AN, Hackney DN, Mesiano S. Pathophysiology of preterm labor with intact membranes. *Semin Perinatol.* 2017;41(7):420-426.
66. Willrich MAV, Braun KMP, Moyer AM, et al. Complement testing in the clinical laboratory. *Crit Rev Clin Lab Sci.* 2021;58(7):447-478.
67. Obeagu EI, Obeagu GU. Neutrophil phenotypes in prolonged labor: Implications for therapeutic strategies. *Medicine.* 2024;103(46):e40611.
68. Obeagu EI. Monocytes at the crossroads of inflammation and labor: biomarker potential in prolonged deliveries - a narrative review. *Ann Med Surg.* 2025;87(12):8361-8368.
69. McCartney SA, Kapur R, Liggitt HD, et al. Amniotic fluid interleukin 6 and interleukin 8 are superior predictors of fetal lung injury compared with maternal or fetal plasma cytokines or placental histopathology in a nonhuman primate model. *Am J Obstet Gynecol.* 2021;225(1):89.e1-89.e16.
70. Singh N, Herbert B, Sooranna G, et al. Is there an inflammatory stimulus to human term labour? *PLoS One.* 2024;16(8):e0256545.

71. Huang Q, Jin XL, Li P, et al. Elevated inflammatory mediators from the maternal-fetal interface to fetal circulation during labor. *Cytokine*. 2021;148(Suppl C).
72. Tissarinen P, Tiensuu H, Haapalainen AM, et al. Elevated human placental heat shock protein 5 is associated with spontaneous preterm birth. *Pediatr Res*. 2023;94(2):1-10.
73. Wang Z, Ou QJ, Gao L. The increased cfRNA of TNFSF4 in peripheral blood at late gestation and preterm labor: its implication as a noninvasive biomarker for premature delivery. *Front Immunol*. 2023;14:1154025.
74. Li T, Yi T, Zhao JT, et al. Combined Proinflammatory Biomarkers Have Better Predictive Value for Term Labor than Single Markers. *Med Sci Monit*. 2019;25:4513-4520.
75. Sui XS, Sui YY, Long PH, et al. Arginase 1 does not affect RNA m6A methylation in mouse fetal lung. *Birth Defects Res*. 2024;116(2):e2318.
76. Ando K, Hédou JJ, Feyaerts D, et al. A Peripheral Immune Signature of Labor Induction. *Front Immunol*. 2021;12:725989.
77. Paul M, Zakar T, Phung J, Gregson A, Barreda AP, Butler TA, Walker FR, Pennell C, Smith R, Paul JW. 20 α -hydroxysteroid dehydrogenase expression in the human myometrium at term and preterm birth: relationships to fetal sex and maternal body mass index. 2023.
78. Akay E, Şirin Donbaloğlu G, Yeniocak AS, et al. Prognostic evaluation of systemic immune inflammatory index and hematological parameters in postpartum hemorrhage: a retrospective analysis. *Ginekol Pol*. 2025;96(4):287-293.
79. Oda T, Tamura N, Ide R, et al. Postpartum acute myometritis suppresses expression of contraction-associated proteins in the gravid uterus. *J Reprod Immunol*. 2024;165:104299.
80. Gallo DM, Romero R, Bosco M, et al. Maternal plasma cytokines and the subsequent risk of uterine atony and postpartum hemorrhage. *J Perinat Med*. 2023;51(2):1.
81. Qu JX, Jiang H, Zhang BY, et al. Oxidative stress-mediated abnormal polarization of decidual macrophages promotes the occurrence of atonic postpartum hemorrhage. *Redox Biol*. 2025;81:103530.
82. Jiang H, Shi HF, Chen L, et al. Is there a relationship between plasma, cytokine concentrations, and the subsequent risk of postpartum hemorrhage? *Am J Obstet Gynecol*. 2022;226(6):835.e1-835.e17.
83. Gallo DM, Romero R, Bosco M, et al. Maternal plasma cytokines and the subsequent risk of uterine atony and postpartum hemorrhage. *J Perinat Med*. 2023;51(2):1.
84. Reitsma SE, Barsoum JR, Hansen KC, et al. Agnostic identification of plasma biomarkers for postpartum hemorrhage risk. *Am J Obstet Gynecol*. 2025;232(2):220.e1-220.e18.
85. Jackson TL, Tuuli MG. Intrauterine Postpartum Hemorrhage-Control Devices. *Obstet Gynecol*. 2023;142(5):1000-1005.
86. Zhang P, Jia YJ, Song H, et al. Novel biomarkers for prediction of atonic postpartum hemorrhage among 'low-risk' women in labor. *Front Immunol*. 2024;15:1416990.