Comparison of the Prognostic Significance of Inflammatory and Thrombotic Indices in Patients with Cardiovascular and Infectious Diseases

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ABSTRACT **Background:** Inflammatory and thrombotic markers play crucial roles in risk stratification for various diseases.

Objectives: To investigate the relative importance of inflammation, measured by C-reactive protein (CRP), and platelet turnover, indicated by immature platelet fraction (IPF), in predicting outcomes for patients with cardiovascular disease, coronavirus disease 2019 (COVID-19), and bacterial infections.

Methods: In this retrospective observational study, we analyzed data from 1473 individuals admitted to the Samson Assuta Ashdod University Hospital between 2018 and 2022. Patients were categorized based on CRP and IPF levels, with a focus on 280 patients in the high CRP/low IPF or high IPF/low CRP tertiles.

Results: The high CRP low IPF group demonstrated significantly higher mortality rates compared to the low CRP high IPF group (13.5% vs. 0.8%, $P < 0.001$). Logistic regression analysis revealed that the high CRP and low IPF combination was the strongest predictor of mortality (odds ratio 12.951, 95% confidence interval 1.409–119.020, $P = 0.024$).

Conclusions: The combination of inflammatory (CRP) and thrombotic (IPF) markers provides superior prognostic information compared to individual disease diagnoses in patients with cardiovascular disease, COVID-19, and bacterial infections.

IMAJ 2025; 27: 442–447

KEY WORDS: C-reactive protein (CRP), immature platelet fraction (IPF), infection, prognostic markers, thrombosis

Inflammatory and thrombotic markers play an important role in the risk stratification of various diseases, particularly cardiovascular disorders and infectious diseases. Many indices of inflammation have been studied and characterized. C-reactive protein (CRP) is one of the most established markers of systemic inflammation in both cardiovascular and infectious disorders [1]. CRP has been shown to have strong prognostic value as well importance for clinical follow-up in patients with atherosclerotic cardiovascular disease, as well as various inflammatory and infectious diseases [2,3].

Immature platelets are young platelets derived from megakaryocytes in the bone marrow. These immature platelets are larger and contain mRNA, allowing them to synthesize more proteins, making them hyper-reactive and pro-thrombotic compared with normal platelets. The immature platelet fraction (IPF) is the percentage of immature platelets among all platelets.

IPF reflects the rate of platelet production and increases in states of high platelet turnover, such as acute myocardial infarction (AMI) and acute infections. IPF has been shown to be a prognostic tool in patients with AMI [4-6] and has significant prognostic value in sepsis, coronavirus disease 2019 (COVID-19), and other infectious diseases [7-11]. For example, IPF levels have been correlated with disease severity in patients hospitalized with COVID-19 [12].

In this study, we investigated the relative importance of inflammation, as measured by CRP, and platelet turnover, indicated by IPF, in predicting clinical outcomes for patients with cardiovascular disease, COVID-19, and bacterial infections. By comparing the prognostic significance of these markers, we sought to determine which prognostic index holds greater significance over time in different patient groups.

PATIENTS AND METHODS

STUDY DESIGN

We analyzed data from individuals admitted to the Samson Assuta Ashdod University Hospital between 2018 and 2022 who had IPF and CRP testing. During the COVID-19 period and following, IPF was routinely tested in the hospital for patients with acute coronary syndromes and patients hospitalized with COVID-19. We identified 1473 potential participants. Exclusion criteria included patients younger than 18 years of age, thrombocytopenia (platelets < 50K), and missing data. The total cohort of patients included 280 individuals and was divided according to IPF tertiles and CRP tertiles. The analysis focused on 280 with high CRP and low IPF or high IPF and low CRP tertiles. These situations represent the extremes of the inflammatory and thrombotic spectrums allowing us to more clearly outline the differences in outcomes and characteristics between patients with predominant inflammation and those with high platelet turnover. This approach enhances biological clarity by isolating distinct physiological states, enabling a more focused analysis of their unique outcomes and characteristics. Statistically, it reduces heterogeneity, increases the signal-to-noise ratio, and minimizes multicollinearity, ensuring that observed associations are both robust and clinically meaningful. By targeting these extremes, we revealed significant patterns that might be diluted in intermediate groups.

DATA COLLECTION

Data were extracted using ICD-9 codes via electronic medical records and included:

- Demographics: age, sex, smoking history, weight, height, and body mass index (BMI)
- Laboratory parameters: hemoglobin (HGB), white blood cell count (WBC), platelet count (PLT), neutrophils (NEU), lymphocytes, albumin, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR)

The primary reasons for hospitalization were categorized as:

- Cardiovascular disease: acute MI, chronic heart failure (CHF), unstable angina, atrial fibrillation (AF)
- Bacterial infections: urinary tract infection (UTI), bacterial pneumonia, septic shock, bacteremia, community-acquired pneumonia with a positive blood culture
- COVID-19

AMI was diagnosed based on the diagnostic criteria recommended by the European Society of Cardiology (ESC). The diagnostic criteria included a combination of clinical symptoms, electrocardiogram findings, and cardiac biomarker levels. Unstable angina was diagnosed based on ESC guidelines, characterized by new onset of severe angina or accelerated angina with no elevation in cardiac biomarkers. CHF was diagnosed based on clinical symptoms and objective evidence of cardiac dysfunction. AF diagnosed by electrocardiogram showing irregular RR intervals and no visible P waves.

UTI diagnosed was based on urinary symptoms and positive urine culture. Pneumonia was diagnosed by clinical symptoms and chest radiograph findings. It was categorized as bacterial based on positive culture or community-acquired pneumonia based on clinical history. Septic shock was diagnosed based on (SOFA score ≥ 2), and need for vasopressors to maintain MAP ≥ 65 mmHg. Bacteremia was diagnosed by positive blood cultures with clinical signs of infection.

COVID-19 was diagnosed based on the World Health Organization case definition, including at least one positive RT-PCR test for SARS-CoV-2 with clinical symptoms.

The category *Other* included all diagnoses that did not meet the specific conditions of cardiovascular disease, bacterial infections, or COVID-19.

IPF levels were evaluated using the Sysmex XN-3000 autoanalyzer (Diamond Diagnostics, USA), which employs fluorescent dyes containing oxazine and ethylene glycol to differentiate between immature and mature platelets. IPF is reported as a percentage, and the immature platelet count (IPC) is calculated by multiplying IPF and the total platelet count. IPF and CRP were measured on admission to the hospital.

STATISTICS

Patients were categorized into two main groups based on their CRP and IPF levels at admission. The low CRP high IPF group consisted of patients with CRP values in the lowest tertile and IPF values in the highest tertile. The high CRP low IPF group included patients with CRP values in the highest tertile and IPF values in the lowest tertile. Normality was tested using Kolmogorov–Smirnov test. Data were analyzed using appropriate statistical methods. Continuous variables are presented using mean, median, interquartile range, and standard deviation (SD) depending on the normality of the data ± SD. A *t*-test or Mann–Whitney were used with normal distribution. Categorical variables were compared using chi-square or Fisher's exact test. Lo-

gistic regression was used to predict mortality based on various factors, including CRP and IPF levels. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25.0 (SPSS, IBM Corp, Armonk, NY, USA).

Table 1. Comparison of patient characteristics and laboratory values low CRP high IPF and high CRP low IPF

Variable	Low CRP high IPF n=132	High CRP low IPF n=148	*P*-value
Demographics			
Age (years)	61 ± 18	70 ± 16	< 0.001
Sex (male)	85 (64.4%)	79 (53.4%)	0.023
Weight (kg)	82.16 ± 16.14	82.34 ± 18.72	0.744
Body mass index (kg/m²)	28.63 ± 5.32	30.07 ± 6.65	0.184
Complete blood count			
Hemoglobin (g/dl)	13.86 ± 1.93	11.71 ± 2.11	< 0.001
WBC (× 10^9/L)	9.23 ± 3.54	10.47 ± 7.06	0.735
Platelets (× 10^9/L)	204 ± 58	263 ± 116	< 0.001
Neutrophils (× 10^9/L)	6.08 ± 3.2	8.5 ± 6.5	< 0.001
Neutrophil to lymphocyte ratio	3.24 ± 2.21	11.33 ± 11.22	< 0.001
Biochemistry			
ALT (U/L)	55 ± 271	43 ± 101	0.878
Albumin (g/dl)	3.99 ± 0.45	3.22 ± 0.57	< 0.001
eGFR (ml/min/1.73 m²)	86.65 ± 36.67	66.19 ± 41.83	< 0.001
Co-morbidities			
Chronic renal failure	14 (10.6%)	31 (20.9%)	0.022
Diabetes type 2	39 (29.5%)	61 (41.2%)	0.046
Dyslipidemia	51 (38.6%)	35 (23.6%)	0.009
Hypertension	69 (52.3%)	85 (57.4%)	0.402
Drugs			
Statins	78 (59.1%)	41 (27.7%)	< 0.001
Antiplatelet	74 (56.1%)	20 (13.5%)	< 0.001
Anticoagulants	34 (25.8%)	21 (14.2%)	0.016
Diagnosis			
Acute MI	46 (34.8%)	4 (2.7%)	< 0.001
STEMI	17 (12.9%)	1 (0.7%)	< 0.001
NSTEMI	26 (19.7%)	2 (1.4%)	< 0.001
COVID-19	2 (1.5%)	75 (50.7%)	< 0.001
Sepsis	1 (0.8%)	19 (12.8%)	< 0.001
Cardiovascular disease	63 (47.7%)	25 (16.9%)	< 0.001
Bacterial infection	4 (3.0%)	59 (39.9%)	< 0.001
Other	83 (62.9%)	32 (21.6%)	< 0.001

ALT = alanine transaminase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, IPF = immature platelet fraction, MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction, WBC = white blood cell count

ETHICS APPROVAL AND PATIENT CONSENT

This study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of Samson Assuta Ashdod University Hospital. Patient consent was waived due to the retrospective nature of the study. All data were anonymized to protect patient privacy.

RESULTS

PATIENT CHARACTERISTICS

Our study included two main groups: low CRP high IPF (n=132) and high CRP low IPF (n=148). The high CRP low IPF group was significantly older (70 ± 15 years vs. 61 ± 18 years, $P < 0.001$) and had a higher proportion of males (54.0% vs. 46.0%, $P = 0.023$) [Table 1].

COMPARISON OF INFLAMMATORY AND THROMBOTIC MARKERS

Significant differences were observed in several hematological parameters, Hemoglobin levels were lower in the high CRP low IPF group (11.58 ± 2.18 g/dl vs. 13.88 ± 1.97 g/dl, $P < 0.001$), platelet count was higher in the high CRP low IPF group (265 ± 120 × 10^9/L vs. 202 ± 57 × 10^9/L, $P < 0.001$). The absolute neutrophil count was higher in the high CRP low IPF (8.65 ± 6.53 × 10^9/L vs. 6.01 ± 3.19 × 10^9/L, $P < 0.001$). The absolute lymphocyte count was lower in the high CRP low IPF group (1.09 ± 0.90 × 10^9/L vs. 2.22 ± 0.99 × 10^9/L, $P < 0.001$). Neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the high CRP low IPF (11.27 ± 10.96 vs. 3.34 ± 2.88, $P < 0.001$) [Table 1].

ASSOCIATIONS WITH CLINICAL OUTCOMES

Analysis of hospital stay duration revealed significant differences between the low CRP high IPF and high CRP low IPF groups across various diagnoses [Table 2]. Notably, patients with AMI in the high CRP low IPF group had significantly longer hospital stays compared to those in the low CRP high IPF group (11 ± 12 days vs. 5 ± 2 days, $P < 0.001$). This trend was consistent when we analyzed patients grouped with cardiovascular disease (10 ± 8 days vs. 5 ± 2 days, $P = 0.05$).

In-hospital mortality rates also differed significantly between the two groups across diagnoses []. The high CRP low IPF group demonstrated higher mortality rates, particularly in patients with cardiovascular disease (24.00% vs. 1.59%, $P < 0.001$) and COVID-19 (13.33% vs. 0%, $P = 0.58$), although the latter did not reach statis-

Table 2. Hospitalizing days by diagnosis

Diagnosis	Low CRP high IPF	High CRP low IPF mean ± SD	*P*-value
Acute MI	5 ± 2	11 ± 12	< 0.001
STEMI	6 ± 3	28*	0.096
NSTEMI	4 ± 2	5 ± 0	0.081
COVID	8 ± 4	7 ± 5	0.653
Sepsis	10*	14 ± 11	0.931
CV disease	5 ± 2	10 ± 8	0.05
Bacterial infection	6 ± 3	10 ± 8	0.562
Other disease	5 ± 6	6 ± 5	0.036

COVID-19 = coronavirus disease 2019, CV = cardiovascular, MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction

*Standard deviation is not applicable (single observation)

Table 3. In-hospital mortality by diagnosis

Diagnosis	Low CRP high IPF count/n (%)	High CRP low IPF count/n (%)	*P*-value
Acute MI	1/46 (2.17%)	0/4 (0%)	0.766
STEMI	0/17 (0%)	0/1 (0%)	Na
NSTEMI	1/26 (3.85%)	0/2 (0%)	0.77
COVID	0/2 (0%)	10/75 (13.33%)	0.58
Sepsis	0/1 (0%)	5/19 (26.32%)	0.55
CV disease	1/63 (1.59%)	6/25 (24.00%)	< 0.001
Bacterial infection	0/4 (0%)	10/59 (16.95%)	0.369
Other	0/83 (0%)	3/32 (9.38%)	0.005
Total	1	20	< 0.001

COVID-19 = coronavirus disease 2019, CV = cardiovascular, MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction

Table 4. Logistic regression analysis predicting mortality

Variable	OR (Exp(B))	95% CI for OR	*P*-value
Sex (male)	1.529	0.542–4.308	0.422
Age (years)	1.066	1.017–1.117	0.008
Bacterial Infection	1.376	0.455–4.164	0.572
CV disease	1.526	0.442–5.267	0.503
Other	0.426	0.088–2.061	0.289
COVID-19	1.063	0.302–3.739	0.925
eGFR	0.991	0.973–1.009	0.314
High CRP low IPF	11.531	1.227–108.378	0.032

95%CI = 95% confidence interval, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CV = cardiovascular, eGFR = estimated glomerular filtration rate, IPF = immature platelet fraction, OR = odds ratio

tical significance due to the small sample size in the low CRP high IPF group.

Logistic regression analysis for predicting mortality revealed that age was a significant predictor of mortality (odds ratio [OR] 1.072, 95% confidence interval] 95%CI 1.024–1.122, $P = 0.003$). The high CRP and low IPF group was the strongest predictor of mortality compared to low CRP high IPF (OR 12.951, 95%CI 1.409–119.020, $P = 0.024$) [Table 4].

Notably, neither bacterial infection, cardiovascular disease, nor COVID-19 were significant independent predictors of mortality in this model.

DISCUSSION

In this retrospective study of a total of 1473 patients, we found that the combination of CRP and IPF levels provides superior prognostic information compared to individual disease diagnoses in patients with cardiovascular disease, COVID-19, and bacterial infections. Our findings highlight the complex interplay between inflammation, thrombosis and platelet turnover in these conditions and suggest that a more comprehensive approach to patient assessment, incorporating both CRP and IPF monitoring, may improve risk stratification and guide treatment decisions.

The high CRP low IPF group demonstrated significantly higher mortality rates compared to the low CRP high IPF group (13.5% vs. 0.8%, $P < 0.001$). This striking difference in outcomes persisted even after adjusting for age, sex, and underlying diagnoses in our logistic regression model (OR 12.951, 95%CI 1.409–119.020, $P = 0.024$). These results suggest that the combination of elevated systemic inflammation and impaired platelet production may identify a particularly high-risk patient population.

Several factors may contribute to the increased mortality observed in the high CRP low IPF group. First, the combination of high CRP and low IPF may reflect a state of severe systemic inflammation that overwhelms the body's compensatory mechanisms, including the ability to produce new platelets. This hypothesis is supported by the significantly higher neutrophil-to-lymphocyte ratio observed in this group (11.27 ± 10.96 vs. 3.34 ± 2.88, $P < 0.001$), a marker previously associated with poor outcomes in various inflammatory conditions [13,14].

In acute inflammatory states, platelets play a crucial role in host defense by secreting immunomodulatory factors and interacting with neutrophils to combat pathogens [15,16]. This process results in significant platelet consumption, potentially leading to thrombocytopenia. Rap-

id restoration of platelet counts is therefore essential for maintaining an effective immune response against infections. Notably, low levels of platelets during septic shock have been associated with increased mortality underlying its effect in combating inflammatory processes [17]. In addition, platelets are essential for preventing hemorrhage in inflamed tissues during thrombocytopenia, highlighting their role in maintaining vascular integrity [18].

The higher mortality observed in the high CRP low IPF group can be explained by the complex interplay between sustained inflammation and bone marrow dysfunction. As discussed by Trompouki and colleagues [19], prolonged exposure to inflammatory signals, such as IFNγ, TNFα, and toll-like receptor ligands, can lead to impaired function of hematopoietic stem and progenitor cells (HSPCs). This inflammatory environment, reflected by high CRP levels, can directly suppress HSPC proliferation and self-renewal, leading to decreased production of mature blood cells, including platelets. The low IPF in this context indicates an inability of the bone marrow to mount an adequate compensatory response through emergency megakaryopoiesis. This failure in platelet production may be due to several factors: direct cytokine-mediated suppression of megakaryocyte progenitors, alterations in the bone marrow microenvironment that disrupt normal hematopoiesis, or exhaustion of HSPCs due to chronic inflammatory stress. Moreover, as Haas and co-authors [20] noted, chronic inflammatory conditions can cause exhaustion of megakaryocytes thus leading to impaired thrombopoiesis. The combination of high systemic inflammation and impaired hematopoietic function, as indicated by the high CRP and low IPF, respectively, likely reflects a state of severe physiological stress and multi-organ dysfunction. This state of sustained inflammation without adequate compensatory hematopoiesis may lead to impaired immune responses, increased susceptibility to infections, and poor overall outcomes, thus explaining the higher mortality in this group.

The higher prevalence of chronic renal failure and diabetes in the high CRP low IPF group likely contributed to the increased mortality risk, as these co-morbidities are known to exacerbate the inflammatory response and impair host defenses. However, after logistic regression analysis the high CRP and low IPF group was the strongest predictor of mortality as compared with low CRP high IPF.

The observed differences in hospital stay duration and in-hospital mortality rates further support the prognostic value of combined CRP and IPF assessment. Patients in the high CRP low IPF group consistently demonstrated longer hospital stays and higher mortality rates across various diagnoses, particularly in cardiovascular disease and COVID-19. These findings suggest that the combination of high systemic inflammation and impaired platelet production may help identify patients at higher risk for prolonged hospitalization and adverse outcomes.

Our findings have several important clinical implications. The strong predictive value of the combined CRP and IPF marker for mortality suggests that these parameters could be used together as a novel risk stratification tool. Patients presenting with high CRP and low IPF should be considered at high risk for adverse outcomes and may benefit from more intensive monitoring and aggressive management.

Moreover, the balance between inflammation and platelet turnover, as indicated by CRP and IPF, could guide anticoagulation strategies, particularly in conditions like COVID-19 where both thrombosis and bleeding are of concern. Future studies should investigate whether tailoring anticoagulation based on these markers could improve outcomes.

CLINICAL IMPLICATIONS

The strong predictive value of the combined CRP and IPF marker suggests that monitoring both these parameters over time could provide valuable insights for risk stratification in patients with cardiovascular disease, COVID-19, and bacterial infections. This approach may allow for more personalized treatment strategies that target both inflammatory and thrombotic pathways.

LIMITATIONS

This study has several limitations that should be considered. First, as a retrospective observational study, our findings are subject to inherent biases and confounding factors that may not have been fully addressed in the analysis. Second, the data were collected at a single medical center, which may limit the generalizability of our findings to other populations or healthcare settings. Third, although our total cohort included 1473 patients, the analysis focused on a subset of 280 patients in the extreme tertiles of CRP and IPF, which may impact the robustness of the results. Fourth, the inclusion of patients with various conditions, such as cardiovascular disease, COVID-19, and bacterial infections, may have introduced variability in the relationships between biomarkers and outcomes across different disease states. Last, the small number of AMI patients (four) in the high CRP low IPF group may limit conclusions specific to this condition, possibly reflecting distinct pathophysiological processes in these patients.

CONCLUSIONS

The combination of inflammatory (CRP) and thrombotic and high platelet turnover (IPF) markers provides superior prognostic information compared to individual disease diagnoses in patients with cardiovascular disease, COVID-19, and bacterial infections. These readily available biomarkers may offer a simple yet powerful tool for risk stratification and could guide clinical decision-making.

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Capsule

A natural experiment on the effect of herpes zoster vaccination on dementia

Eyting and colleagues aimed to determine the effect of live-attenuated herpes zoster vaccination on the occurrence of dementia diagnoses. Using large-scale electronic health record data, the authors showed that the percentage of adults who received the vaccine increased from 0.01% among patients who were merely 1 week too old to be eligible, to 47.2% among those who were just 1 week younger. Apart from this large difference in the probability of ever receiving the zoster vaccine, individuals born just 1 week before 2 September 1933 are unlikely to differ systematically from those born 1 week later. Using these comparison groups in a regression discontinuity design, they showed that receiving the zoster vaccine reduced the probability of a new dementia diagnosis over a follow-up period of 7 years by 3.5 percentage, corresponding to a 20.0% relative reduction. This protective effect was stronger among women than men. Using a unique natural experiment, this study provides evidence of a dementia-preventing or dementia-delaying effect from zoster vaccination that is less vulnerable to confounding and bias than the existing associational evidence.

Nature 2025; 641: 438
Eitan Israeli