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Serology and Comorbidities in Patients with Fracture Nonunion: A Multicenter Evaluation of 640 Patients

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Abstract

Introduction: This multicenter cohort study investigated the association of serology and comorbid conditions with septic and aseptic nonunion.

Methods: From 1/1/11 to 12/31/17, consecutive individuals surgically treated for nonunion were identified from seven centers. Nonunion type, comorbid conditions and serology were assessed.

Results: 640 individuals were included. 57% were male with a mean age of 49 years. Nonunion sites included tibia (35.2%), femur (25.6%), humerus (20.3%), and other less frequent bones (18.9%). Types of nonunion included septic (17.7%) and aseptic (82.3%). Within aseptic, nonvascular (86.5%) and vascular (13.5%) nonunion were seen. Rates of smoking, alcohol abuse, and diabetes mellitus were higher in our nonunion cohort compared to population norms. Coronary artery disease and tobacco use associated with septic nonunion ($p < 0.05$). Bisphosphonates were associated with vascular nonunion ($p < 0.05$). Serologically, increased ESR, CRP, PTH, RDW, MPV, and platelets and decreased ALC, hemoglobin, MCH, MCHC, and albumin were associated with septic while lower calcium associated with nonvascular nonunion ($p < 0.05$). The presence of four or more of increased ESR, CRP, or RDW, decreased albumin, and age under 65 years carried an 89% positive predictive value for infection. Hypovitaminosis D was seen less frequently than reported in the general population, while anemia was more common. However, aside from hematologic and inflammatory indices, no other serology was abnormal more than 25% of the time.

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Discussion: Abnormal serology and comorbid conditions including smoking, alcohol abuse, and diabetes mellitus, are seen in nonunion; however, serologic abnormalities may be less common than previously thought. Septic nonunions are associated with inflammation, younger age, and malnourishment. Based on observed frequency of abnormality, routine lab work is not recommended for nonunion assessment; however, specific focused serology may help determine the presence of septic nonunion.

Introduction

Fracture healing is a complex process that involves adequate mechanical stability, bony contact, blood supply, and appropriate endocrine and metabolic processes. When there is an insult to any of these areas, a solid union at the fracture site may not occur without further intervention.[1] The overall incidence of nonunion is estimated at 5–10%.[2] While the US Food and Drug administration defines a nonunion as a fracture that is at least 9 months old and has not shown any signs of healing for three consecutive months[3] Brinker and O'Connor define nonunion without an indication for temporality. Instead, they rely on the opinion of the treating physician to determine when there is no possibility of healing without further intervention.[1]

The routine ordering of laboratory studies has become a standard of practice to evaluate for medically reversible causes of nonunion. Brinker et al. 2007 established an association between endocrine or metabolic abnormalities and nonunion through laboratory testing in 37 patients.[2] Despite there being significant research into the area of nonunion, there remains many gaps in our knowledge, conflicting evidence, and few guidelines supporting the now routine ordering of lab studies.

Therefore, the aims of this study were to identify and compare rates of abnormal serology and medical comorbidities in patients with septic and aseptic nonunion, compare this to the general population, and develop a tool to predict septic nonunion through a large multicenter retrospective study. We hypothesized that serologic, metabolic, and endocrinologic abnormalities and medical comorbidities are seen commonly in nonunion and can be used to predict the presence of a septic nonunion.

Materials and Methods

Institutional Review Board approval was obtained from all participating sites prior to the initiation of the study. From 1/1/11 – 12/31/17, patients who presented for corrective surgery of nonunion of the clavicle, humerus, radius, ulna, metacarpal, pelvis and acetabulum, femur, patella, tibia, calcaneus, tarsal, and metatarsal were retrospectively investigated by the following CPT codes: 23485, 24430, 24435, 25400, 25405, 25415, 25420, 25431, 25440, 27470, 27472, 27720, 27722, 27724, 27725, 27726, 28320, 28322. Fractures of the scaphoid, femoral neck, talar neck, and 5th metatarsal were excluded. Pathologic fractures due to oncologic disease were also excluded. Nonunion was diagnosed by the treating surgeon and characterized as septic or aseptic with the latter subdivided into vascular or nonvascular types[4].

Demographics, co-morbid conditions, and serologic assessments were determined at the time of nonunion diagnosis. The extent of serologic assessment was determined by the treating surgeon, following the guidelines set forth previously by Brinker. Serology included thyroid stimulating hormone (TSH), parathyroid hormone (PTH), 25-hydroxy cholecalciferol (25OH D), calcium (Ca), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), platelets, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and albumin. Septic nonunion was defined as a positive culture from the operating room. Data was entered retrospectively by an independent researcher from each institution and pooled into a single database.

Patient demographic characteristics, comorbidities, medications, and laboratory indices were described in frequencies and percentages when the variables were categorical and in means and standard deviations when the variables were continuous. Two-sided Fisher's exact tests and two-sample t-tests were used to test the difference between septic and aseptic, as well as between vascular and nonvascular nonunions, when appropriate. In the planning stage, we anticipated that a study with 600 patients (100 septic vs. 500 aseptic) would have more than 80% power to detect a binary outcome of 46% in the septic group, compared with 30% in the aseptic group under a 5% type-I error rate. For a continuous outcome, the proposed sample size could reach an 80% power if the effect size was larger than 0.31 in Cohen's d.

Stepwise Akaike information criteria were utilized to select variables in the multivariate logistic regression to associate covariates to the presence of infection. Collinearity between covariates in the serology data was likely; however, since the collinearity had little effect in prediction in our model, we maintained the covariate's original scale without combination or transformation. Ultimately, a scoring system to predict infection was developed, and we utilized a decision tree[5] to determine the best cutoff of the scores. We reported positive predictive values (precision) and sensitivity (recall) for the model's prediction performance. The model was further validated by leave-one-out cross-validation to demonstrate the model's out-of-bag predictability. The leave-one-out cross-validation showed the same prediction performance, demonstrating the robustness of our classifier. A complete-case analysis for missing data was utilized since there was no apparent evidence the data was missing not at random. Statistical analysis was conducted using R 4.0.2 (R Core Team, 2020).

Results

Seven hundred and thirty nine patients were identified by CPT code across the seven Level 1 Trauma Centers, which contributed 67, 132, 50, 140, 130, 47, and 221 patients, respectively. Ultimately, 640 patients met final inclusion criteria. Of these, the treating surgeon diagnosed 113 (17.7%) with a septic nonunion and 527 (82.3%) with aseptic nonunion. Within aseptic nonunion, 71 (13.5%) were diagnosed with vascular nonunion and 456 (86.5%) with nonvascular nonunion. At the time of nonunion diagnosis, the average age was 48.7 years. Sex distribution was 353 (56.6%) male and 271 (43.4%) female. The average BMI

in the study sample was 29.9, 35.6% were current smokers, and 12.2% reported a history of alcohol abuse. 506 (79.1%) fractures were treated with initial ORIF, while 134 (20.9%) were initially treated nonoperatively. A minority of patients (30.3%) were multiply operated on in addition to the original form of surgical or nonsurgical treatment and nonunion surgery [Range, 1 to 8 additional operations]. No bone investigated was more likely to become infected or undergo a vascular or nonvascular nonunion ($p > 0.05$).

Nonmodifiable and modifiable (the authors recognize that these factors are usually not modifiable prior to the patient's presentation with fracture or nonunion, but do have the potential for optimization when fracture or nonunion is diagnosed and were therefore characterized as modifiable) risk factors are presented in Table 1 and 2, respectively. Younger age, male sex, and presence of open fracture associated with septic nonunion. No nonmodifiable factor differentiated nonvascular from vascular nonunion ($p > 0.597$). Coronary artery disease and tobacco use associated with septic nonunion, but no medical comorbidity differentiated nonvascular from vascular nonunion. Alcohol abuse trended toward a statistically significant association with septic nonunion ($p = 0.057$).

Modifiable risk factors were compared to population norms in the United States. Smoking (35.6% vs. 13.7%)[6], diabetes mellitus (19.2% vs. 9.8%)[6], and alcohol abuse (12.2% vs. 5.3%)[6] were observed to be higher in nonunion patients than in the general US population, while the rate of obesity (42.0% vs 40.6%)[6], severe obesity (10.2% vs 8.4%)[6], heart failure (5.0% vs. 2.4%)[6], hypertension (45.5% vs. 47.3%)[6], coronary artery disease (6.9% vs. 7.2%)[6], stroke (2.7% vs 2.7%)[6], chronic obstructive pulmonary disease (8.8% vs. 6.4%)[7], and liver failure (0.9% vs. 1.8%)[8] were similar, and the rate of renal disease was lower (5.9% vs. 14.8%).[6]

Medications taken by patients prior to nonunion ORIF were analyzed (Table 3). Notably, NSAIDs, disease-modifying antirheumatic drugs (DMARDs), antiepileptic, statins, and antacids were evenly distributed among nonunion types. Individuals who took bisphosphonates were more likely to have a vascular nonunion.

Table 4 shows average values from a comprehensive serologic assessment of nonunion. Increased MPV (49.9%), ESR (37.2%), CRP (21.0%), PTH (24.5%), RDW (20.0%), and TSH (19.0%) were seen. Decreased hemoglobin (29.2%), ALC (24.4%) and ANC (15.1%), 25-OH D (22.3%), albumin (19.4%), and calcium (25.3%) were also present. Septic nonunion was associated with increased ESR, CRP, PTH, RDW, MPV, and platelets and decreased ALC, hemoglobin, MCH, MCHC, and albumin while lower calcium associated with nonvascular nonunion ($p < 0.05$). The extent of serologic analysis was determined by the treating surgeon so as to capture routine practice management. Inherent to this, not every surgeon obtained a comprehensive serologic analysis, and due to laboratory variations, not all biomarkers were captured by the same laboratory order. For example, a complete blood count (CBC) was obtained in 91.1% of patients, but laboratory facility differences accounted for missing MPV in 57.3% of CBCs obtained. Additionally, although calcium was obtained in 84.1% of patients, a reflex order for PTH was obtained in only 29.8% based on the presence of hypo- or hypercalcemia. Consequently, 3.8% captured all 19 serologic biomarkers, 33.9% captured at least 16 biomarkers, and 89.2% captured at least 10

biomarkers. The least commonly included biomarkers were 25OH D (41.3%), TSH (39.7%), and PTH (29.8%). CRP was obtained in 51.4% and ESR in 45.3%.

Although 82.4% had at least one serologic abnormality, the predominant abnormal values (Table 5) were associated with inflammation rather than malnourishment or metabolic derangement. Aside from routine hematologic and inflammatory serology, no serologic biomarker was abnormal in more than 25% of patients. Hypovitaminosis D was seen in only 22% of the cohort compared to 41.6% in the general US population.[9] Anemia was seen in 29% of the cohort and 40% of those with septic nonunion ($p < 0.05$) compared to an estimated 5.6% of the US population.[10] Elevated RDW was seen in 20% of the cohort compared to an estimated 6.25%[11] of the US population. Abnormal TSH was seen in 19% of the cohort compared to an estimated 0.3% with hypothyroidism[12] and 1.3% with hyperthyroidism[13]. A comparison for other biomarkers is not reported here due to due to wide variations in serology in acute and chronic disease settings.

A model for predicting septic nonunion that incorporated the presence of a serologic inflammatory response, malnutrition, and age was developed. The presence of four or more of the following risk factors carried an 89% positive predictive value and 29% sensitivity for septic nonunion: (1) ESR [0 – 20 mm/hr] increased, (2) CRP [0 – 10 mg/L] increased, (3) RDW [12 – 15%] increased, (4) Albumin [3.5 – 5.5 g/dL] decreased, (5) Age < 65 years. The combination of elevated ESR, CRP, and WBC [$4.5 – 11.0 \times 10^9$/L] was rare (2.65% of all septic nonunions), and elevated WBC in isolation, did not differentiate septic from aseptic nonunion.

Discussion

The development of fracture nonunion is multifactorial and despite extensive research is not well understood. Nonunion can be influenced by modifiable and non-modifiable factors, and our study was able to help characterize this. In our cohort, non-modifiable risk factors such as younger age and presence of an open fracture associated with septic nonunion, while the bone that was fractured, sex, and race did not vary among nonunion types. Modifiable risk factors, including smoking or alcohol abuse, and serologic abnormalities related to inflammation and malnourishment associated with septic nonunion.

Prior studies have attempted to elucidate risk factors for nonunion. While increasing severity of soft tissue injury can have an appreciably higher rate of nonunion[14], the majority of proposed or accepted risk factors predate the trauma including nicotine abuse[3,15–17], systemic medical conditions such as diabetes, obesity, and metabolic bone disease, and use of certain medications.[1,18] Modifiable risk factors including smoking, diabetes mellitus, and alcohol abuse were seen at higher rates in our nonunion cohort than is seen in the general US population, while rates of CHF, CAD, COPD, renal failure, liver failure, and obesity were observed at similar or lower rates than what is estimated in the general US population. In line with the 2019 OTA Clinical Practice Guidelines which supported the use of NSAIDs as part of a comprehensive analgesic plan without concern for increased risk of nonunion[19], our cohort demonstrated no propensity for vascular or nonvascular nonunion with the use NSAIDs. Additionally, bisphosphonate use was associated with vascular nonunion.

Malnutrition is thought to be associated with nonunion, as metabolic requirements increase during fracture healing[20–25]. Albumin and ALC have been suggested previously as laboratory indices for malnutrition[23,24] and RDW is a known marker of the chronic inflammatory state and the metabolic syndrome[25]. Although hypoalbuminemia, lymphopenia, and elevated RDW were found in the minority of our nonunion cohort (19%, 24%, and 20%, respectively); the three were identified as serologic risk factors for infection, and the rates of anemia, elevation of RDW, and abnormal TSH were more prevalent in our nonunion cohort compared to the general US population. This suggests that malnutrition may be implicated in septic nonunion and perhaps the failure of fracture healing all-together. Nevertheless, Vitamin D and calcium were abnormal in only 22% and 25% of our nonunion cohort, respectively and hypovitaminosis D was less prevalent in our nonunion cohort than in the general US population (the authors recognize that this may iatrogenic due to widespread vitamin D supplementation by orthopaedic surgeons). In support of this, a randomized control trial concluded that fracture union was independent of vitamin D supplementation even in those with hypovitaminosis D.[26] Although many laboratory indices previously proposed by Brinker[2] were found to be abnormal, our data shows that nearly four out of every five nonunion patients will have normal values of TSH, PTH, 25-OH vitamin D, calcium, ALC, or albumin. Only two serologic markers – RBC and MPV (a marker of chronic inflammation)[27] – were abnormal more than 50% of the time and no other marker was abnormal in more than 37% of patients. Excluding RBC and MPV, 71.2% patients at least one serologic abnormality.

Assessing probability of infection is critical when treating nonunion. While the gold standard diagnosis remains positive intraoperative cultures, comprehensive evaluation is important and controversy exists in the appropriate preoperative serologic assessment[27–32]. We have presented a scoring system that suggests that a combination of at least four of the following: age less than 65, elevated ESR and CRP representing an inflammatory state, elevated RDW, and hypoalbuminemia is sufficient to predict septic nonunion. This algorithm should act as an adjunct to the diagnosis and expeditious treatment of septic nonunion, but should not replace the gold standard diagnosis of positive intraoperative cultures or a draining sinus. Absence of these markers does not rule out infection, and the surgeon should use his or her judgement to guide intraoperative microbiological assessment.

From the results of this study, the authors emphasize that the use of broad serologic assessment in the workup of aseptic nonunion has a lower yield than previously described. Although it is possible that a subset of patients with known endocrinopathy may benefit from serologic correction and optimization[2], there is insufficient data to justify the cost of a routine laboratory assessment, which is approximately $519 at the lead institution. Rather, the authors recommend selective serologic assessment in patients undergoing workup of septic nonunion including CBC with differential ($35), ESR ($14), CRP ($33), and albumin ($27), but cannot refute Brinker's[2] recommendation for consultation with an endocrinologist when endocrinopathy is present. Importantly, we must recognize an extensive number of patients with normal serology and without metabolic derangement do suffer from fracture nonunion and that abnormal serology should not be solely to blame for the progression to nonunion. However, it is evident that some form of malnutrition may be a contributing factor.

There are limitations to this study. Without a matched control group of patients who achieve fracture union, it is impossible to predict risk factors for nonunion based on serology, fracture characteristics, and patient factors. Inherent to a retrospective study in which the treating surgeon determined the extent of serologic assessment, there are patients with missing serologic biomarkers. To account for this, the model was validated by the leave-one-out cross-validation to demonstrate the model's out-of-bag predictability, and a complete-case analysis for missing data was utilized since there was no evidence for missing data not at random. As with all retrospective reviews, this study was limited by the data which was input; however, the strength of a large number of patients should make these conclusions pertinent to clinical practice. This study was designed to only look at the associations with patients who presented with nonunion to examine whether the use of routine lab work was justified and not to determine risk factors or causality. The authors recognize that some patients with abnormal serology and multiple comorbidities heal their fractures while some patients with normal serology and no comorbidities do not. Accordingly, depending on serology correction while delaying or avoiding appropriate surgical care could be fraught with less than optimal results.

Abnormal serology was not as prevalent as might be expected, suggesting other etiologies for failure of fracture healing. However, rates of smoking, diabetes mellitus, and alcohol abuse were observed to be higher in our cohort compared to the general US population suggesting a role for primary and secondary preventive measures in these patients. Septic nonunions were highly associated with elevated inflammatory markers, younger age, and a chronic malnourished state, and this serology should be assessed when septic nonunion is suspected but not yet confirmed. Further research should be directed at attempting to identify true risk factors for the development of nonunion, but based on our analysis the authors cannot convincingly recommend routine serologic assessment of nonunion prior to surgical intervention other than to rule out infection.

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Table 1.

Nonmodifiable Risk Factors presented as mean (SD) or n (%) of patients in the total, septic, and aseptic cohorts. Younger age, male sex, and presence of open fracture associated with septic nonunion. No nonmodifiable factor differentiated nonvascular from vascular nonunion (p > 0.597)

Nonmodifiable Risk Factors	Total (n = 640)	Septic (n = 113)	Aseptic (n = 527)	p-value
Age (y)	48.7	45.3	49.0	0.018
Sex (m)	353 (56.6)	75 (66.4)	278 (54.4)	0.021
Race				
African American	85 (13.4)	17 (15.0)	68 (13.0)	0.604
Caucasian	500 (78.6)	92 (81.4)	408 (78.0)	
Other	51 (8.0)	4 (3.5)	47 (9.0)	
Open Fractures	40 (6.3)	16 (14.2)	24 (4.6)	<0.001

y = years; m = male

Table 2.

Modifiable risk factors presented as mean (SD) or n (%) of patients in the total, septic, and aseptic cohorts. Of medical comorbidities, CAD and tobacco use associated with septic nonunion, but no medical comorbidity differentiated nonvascular from vascular nonunion. Alcohol abuse trended toward association with septic nonunion (p = 0.057).

Modifiable Risk Factors	Total (n = 640)	Septic (n = 113)	Aseptic (n = 527)	p-value
Diabetes Mellitus	123 (19.2)	21 (18.6)	102 (19.4)	0.896
Heart Failure	32 (5.0)	5 (4.4)	27 (5.1)	1.000
CAD	44 (6.9)	13 (11.5)	31 (5.9)	0.040
COPD	56 (8.8)	13 (11.5)	43 (8.2)	0.271
Stroke	17 (2.7)	5 (4.4)	12 (2.3)	0.200
Liver Failure	6 (0.9)	1 (0.9)	5 (0.9)	1.000
Renal Failure	36 (5.9)	8 (7.1)	28 (5.3)	0.498
Cancer	48 (7.5)	4 (3.5)	44 (8.3)	0.112
Hypertension	291 (45.5)	53 (46.9)	238 (45.2)	0.756
Hyperlipidemia	115 (18.0)	22 (19.5)	93 (17.6)	0.685
Tobacco Use	228 (35.6)	53 (46.9)	175 (33.2)	0.007
Alcohol Abuse	78 (12.2)	20 (17.7)	58 (11.0)	0.057
BMI (kg/m ^{2})	29.9	29.4	30.0	0.441

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; BMI = body mass index

Table 3:

Medications taken by nonunion type presented as n (%) of patients in the total, septic, aseptic, nonvascular, and vascular cohorts. Bisphosphonate use associated with aseptic vascular nonunion. No other medication associated with septic, nonvascular, or vascular nonunion.

Medication	Total (n = 640)	Septic (n = 113)	Aseptic (n = 527)	p-value	Nonvascular (n = 456)	Vascular (n = 71)	p-value
NSAID	229 (35.8)	44 (38.9)	185 (35.1)	0.450	161 (35.3)	24 (33.8)	0.894
DMARD	23 (3.6)	4 (3.5)	19 (3.6)	1.000	16 (3.5)	3 (4.2)	0.732
Bisphosphonates	20 (3.1)	3 (2.7)	17 (3.2)	1.000	9 (2.0)	8 (11.3)	<0.001
Psychotropic	214 (33.4)	42 (37.2)	172 (32.6)	0.380	145 (31.8)	27 (38.0)	0.341
Antiepileptic	63 (9.8)	6 (5.3)	57 (10.8)	0.082	47 (10.3)	10 (14.1)	0.312
Statin	125 (19.5)	20 (17.7)	105 (19.9)	0.695	92 (20.2)	13 (18.3)	0.873
Antacid	145 (22.7)	27 (23.9)	118 (22.4)	0.712	97 (21.3)	21 (29.6)	0.127
Steroids	34 (5.3)	4 (3.5)	30 (5.7)	0.489	25 (5.5)	5 (7.0)	0.582

NSAID = nonsteroidal anti-inflammatory drug; DMARD = disease modifying anti-rheumatic drug

Table 4.

A comprehensive serologic assessment is presented by nonunion type as mean (SD).

Serology	Total	Septic	Aseptic	p-value	Nonvascular	Vascular	p-value
TSH [0.6–3.3uIU/mL]	2.3 (4.7)	2.1 (1.2)	2.3 (5.0)	0.844	2.3 (5.3)	2.2 (1.4)	0.936
PTH [12–72 pg/mL]	58.7 (91.0)	134.2 (256.2)	49.4 (27.4)	0.145	49.0 (25.5)	51.5 (36.6)	0.674
25OH D [20–100 ng/mL]	33.4 (18.0)	31.1 (12.5)	33.7 (18.6)	0.464	33.6 (18.4)	34.1 (20.2)	0.904
Ca [8.5–10.2 mg/dL]	9.2 (1.4)	8.9 (1.1)	9.2 (1.5)	0.103	9.2 (1.5)	9.5 (0.8)	0.030
ESR [0–20 mm/hr]	24.2 (24.1)	36.0 (28.3)	19.3 (20.1)	<0.001	19.4 (20.3)	18.7 (19.6)	0.863
CRP [0–10 mg/L]	11.6 (33.7)	18.1 (40.0)	8.8 (30.3)	0.039	9.0 (31.6)	7.7 (22.4)	0.806
WBC [4.5–11 10*9/L]	8.2 (3.9)	8.4 (3.0)	8.2 (4.1)	0.672	8.3 (4.3)	7.6 (2.2)	0.267
RBC [4.5–5.9 10*12/L]	4.4 (0.7)	4.3 (0.7)	4.4 (0.7)	0.150	4.4 (0.7)	4.4 (0.6)	0.857
HGB [12–17.5 g/dL]	12.9 (2.1)	12.4 (2.3)	13.0 (2.0)	0.003	13.0 (2.0)	13.0 (2.1)	0.995
HCT [34.9–50%]	38.9 (6.3)	37.9 (5.9)	39.1 (6.4)	0.069	39.1 (6.5)	39.3 (5.7)	0.797
MCV [80–100 fL]	89.0 (7.3)	87.9 (6.9)	89.3 (7.4)	0.075	89.3 (7.7)	89.5 (5.0)	0.835
MCH [26–34 pg]	29.5 (2.4)	28.5 (3.1)	29.7 (2.2)	<0.001	29.7 (2.2)	29.6 (2.0)	0.691
MCHC [31–37 g/dL]	33.0 (1.3)	32.6 (1.5)	33.1 (1.3)	<0.001	33.1 (1.2)	33.1 (1.3)	0.641
RDW [12–15%]	14.1 (1.6)	14.9 (1.9)	13.9 (1.5)	<0.001	13.9 (1.5)	13.9 (1.6)	0.959
MPV [7–10 fL]	9.9 (1.3)	9.5 (1.6)	10.0 (1.3)	0.008	10.0 (1.2)	9.9 (1.7)	0.797
Platelets [150–450 10*3/mL]	265.2 (90.3)	290.4 (100.9)	259.4 (86.8)	0.004	259.2 (89.9)	260.8 (60.8)	0.892
ANC [2–7.5 10*9/L]	4.9 (2.2)	5.4 (2.7)	4.8 (2.0)	0.051	4.8 (2.1)	4.9 (1.8)	0.719
ALC [1.5–5 10*9/L]	2.0 (0.8)	1.9 (0.7)	2.1 (0.8)	0.039	2.1 (0.8)	2.1 (0.6)	0.757
Albumin [3.5–5.5 g/dL]	3.9 (0.6)	3.5 (0.7)	4.0 (0.6)	<0.001	4.0 (0.6)	3.9 (0.6)	0.434

TSH = thyroid stimulating hormone; PTH = parathyroid hormone; 25OH D = 25-Hydroxy Vitamin D; Ca = Calcium; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = White blood cell count; RBC = red blood cell count; HBG = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; RDW = red cell distribution width; MPV = mean platelet volume; ANC = absolute neutrophil count; ALC = absolute lymphocyte count

Table 5.

Serology is presented by percent abnormal as n (%) of patients in the total, septic, aseptic, nonvascular, and vascular cohorts. n is the total number of patients who were assessed for the biomarker. Aside from routine hematologic and inflammatory serology, no serologic marker was abnormal in more than 25% of patients.

Serology	n	Total	Septic	Aseptic	Nonvascular	Vascular
TSH	254	49 (19)	7 (23)	42 (19)	32 (17)	10 (35)
PTH	192	47 (25)	8 (38)	39 (23)	32 (22)	7 (27)
25OH Vit D	264	59 (22)	5 (17)	54 (23)	43 (21)	11 (37)
Ca	538	136 (25)	22 (23)	114 (26)	106 (27)	8 (15)
ESR	290	108 (37)	53 (62)	55 (27)	46 (27)	9 (27)
CRP	329	69 (21)	38 (38)	31 (14)	26 (14)	5 (14)
WBC	583	110 (19)	23 (21)	87 (18)	79 (19)	8 (14)
RBC	577	310 (54)	66 (61)	244 (52)	218 (53)	26 (46)
Hgb	583	170 (29)	43 (40)	127 (27)	110 (26)	17 (29)
Hct	573	133 (23)	32 (31)	101 (22)	91 (22)	10 (17)
MCV	583	51 (9)	14 (13)	37 (8)	34 (8)	3 (5)
MCH	581	47 (8)	20 (19)	27 (6)	24 (6)	3 (5)
MCHC	581	32 (6)	13 (12)	19 (4)	15 (4)	4 (7)
RDW	580	116 (20)	43 (40)	73 (15)	60 (15)	13 (22)
MPV	335	166 (50)	29 (41)	137 (52)	117 (52)	20 (56)
Platelets	580	55 (10)	14 (13)	41 (9)	40 (10)	1 (2)
ANC	324	49 (15)	16 (21)	33 (13)	29 (13)	4 (13)
ALC	324	79 (24)	23 (30)	56 (23)	50 (23)	6 (19)
Albumin	341	66 (19)	27 (39)	39 (14)	33 (14)	6 (18)