Original Research Article

Diagnostic Use of Serum Ferritin as a Predictor of Hospital Outcome at Admission in Patients with Infective Endocarditis

Abstract

Background: Infective endocarditis (IE) is characterised by a concentration of infection inside the heart; it is caused by a bacterial or fungal infection of the endocardial surface of the heart; and it is linked with substantial morbidity and death. The aim of this research was to assess serum ferritin as an admission predictor of in-hospital prognosis in subjects with IE.

Methods: This case control research included 60 subjects diagnosed with IE on the basis of the modified duke's criteria. Subjects were allocated equally into two groups: group I: IE subjects who were further subdivided into two groups based on presence or absence of major adverse cardiovascular events (subgroup A: 19 patients who showed IE complications or major adverse cardiac events during hospitalization and subgroup B: 11 patients who showed a smooth course during hospitalization without major adverse cardiac events or IE complications) and IE subjects as well as age and sex matched 30 healthy subjects.

Results: serum ferritin level were significantly increased in group I than group II (P value <0.05). Serum ferritin level was significantly increased in subgroup A than subgroup B (P value <0.001). serum ferritin can significantly predict bad outcome (P value <0.001) with AUC of 0.964 (95% CI: 0.881 – 0.995). At cut off >1200, serum ferritin can significantly predict bad outcome with 94.44% sensitivity, 92.86% specificity, 85% PPV and 97.5% NPV.

Conclusions: Serum ferritin was significantly increased in IE subjects who experienced problems on admission as compared to IE subjects who didn't.

Keywords: Serum Ferritin, Infective Endocarditis, Echocardiography

Introduction:

Infective endocarditis (IE) is characterised by a concentration of infection inside the heart; it is caused by a bacterial or fungal infection of the endocardial surface of the heart; and it is linked with substantial morbidity and death [1].

IE mainly affects young or middle-aged persons with underlying rheumatic heart disease (RDH) or congenital heart disease, hemodialysis, prosthetic valve replacement, immunosuppression, venous catheters, and intravenous (IV) drug abusers have emerged as the major risk factors [2, 3].

Concurrently, staphylococci and streptococci and enterococci are the main causal agent but also less prevalent pathogens as Candida species and Pseudomonas aeruginosa leading to formation of a mature vegetation [4].

The American Heart Association (AHA) released recommendations advocating antibiotic prophylaxis for subjects with RDH and coronary heart disease (CHD) having dental extraction, as well as the maintenance of excellent oral hygiene for high-risk populations [5].

IE should be suspected in any case with idiopathic fevers, night sweats, or systemic disease symptoms, especially if any of these risk factors are exist: a structural or congenital heart disease, prosthetic heart valve, IV drug use, and a current history of invasive techniques (e.g., wound care, hemodialysis). In a clinical history suggestive of IE, a past heart lesion and an indications of current source of bacteremia are present [6].

IE consequences include cardiac, musculoskeletal, renal, neurologic, and pulmonary troubles, in addition to systemic infection consequences as metastatic infection, embolization, and mycotic aneurysm. Multiple complications may develop concurrently [7].

Reaching a quick and precise diagnosis in suspected IE cases is a main obstacle of the illness, the modified Duke criteria, initially developed for research objectives and recommended by AHA guidelines for assessment of suspected IE cases [8, 9].

Echocardiography represents an important component of imaging as it's speed and simplicity in many cases. All cases with a moderate or strong suspicion of IE should undergo diagnostic transthoracic echocardiography (TTE) to identify valvular abnormalities [10].

For the signs of increasing valve and tissue damage, high risk of embolism, and uncontrolled infection, surgery is undertaken. Currently, 50% to 60% of subjects get surgery, and six-month survival rates climbs to 80% after operation [11, 12].

Serum ferritin is an iron-containing blood protein that was identified in 1937 by Lauf-berger and initially detected in serum using a radioimmunoassay technique [13]**.** In addition to being utilized as an indicator of iron accumulation in the body, ferritin is also utilized as an acute phase reactant to inflammation [14].

Serum ferritin was shown to be one of the greatest predictors of cardiovascular disease presence and development [15]. The normal blood ferritin range is 24 to 336 µg/L for men whereas 11 to 307 µg/L for women.

The aim of this research was to assess serum ferritin as an admission predictor of in-hospital prognosis in subjects with IE.

Patients and Methods:

This case control research included 60 subjects diagnosed with IE on the basis of the modified duke's criteria.

An informed written consent was obtained from all participants in the research. Ethical committee approval and informed consent were obtained from all subjects involved in this research, and any unanticipated dangers that arose throughout the investigation were disclosed to the subjects and the ethical committee on time, taking in sight the patients' privacy and confidentially of the data.

Exclusion criteria were patients of dilated cardiomyopathy, patients of chronic kidney diseases, patients of chronic liver diseases, patients of malignancy, patients of systemic lupus erythematosus, patients of rheumatoid arthritis and patients with active Covid-19.

Subjects were allocated equally into two groups: group I: IE subjects who were further subdivided into two groups based on presence or absence of major adverse cardiovascular events (subgroup A: 19 patients who showed IE complications or major adverse cardiac events during hospitalization and subgroup B: 11 patients who showed a smooth course during hospitalization without major adverse cardiac events or IE complications) and IE subjects as well as age and sex matched 30 healthy subjects.

All subjects underwent full history taking and clinical investigation (vital signs: heart rate, blood pressure (BP), respiratory rate and temperature), general examination, skin examination, abdominal examination (splenomegaly and hepatomegaly), local cardiac examination (abnormal pulsation, heart sounds and murmurs), standard supine 12 lead ECG, Blood tests (CBC, urea/creatinine, serum ferritin, CRP, blood culture and virology), TTE and imaging (CT Chest, abdominopelvic US, CT brain and fundus examination).

Major adverse cardiovascular events were recognized as heart failure, myocardial infraction, stoke, ventricular arrythmia and sudden cardiac death.

Complications of IE were identified as stroke, heart failure, mycotic aneurysm, pulmonary embolism, renal failure, sepsis, myocardial infarction and sudden cardiac death.

Prediction of poor outcome in IE: older age, diabetes mellitus, heart failure, renal failure, cerebral stroke, septic shock and large vegetations**.**

Statistical analysis

SPSS v26 was utilized to do statistical analysis (IBM Inc., Chicago, IL, USA). Comparing the two groups utilizing an unpaired Student's t-test and the two subgroups utilizing a paired Student's t-test, quantitative variables were provided as mean and standard deviation (SD).

When applicable, qualitative variables were given as frequency and percentage (%) and examined utilizing the Chi-square test or Fisher's exact test. A two-tailed P value ≤ 0.05 was deemed statistically significant.

Results:

Smoking, family history, cardiac history, IV drug addicts heart rate, respiratory rate and temperature and serum ferritin level were significantly increased in group I than group II (P <0.05). Systolic BP was significantly decreased in group I (P =0.019). Age, sex and diastolic BP were insignificantly different between both groups. Table 1

Table 1: Demographic data, risk factors, vital signs and serum ferritin level of the studied patients

		Group I (N = 30)	Group II (N = 30)	P value
Age (years)		39.63 ± 12.37	38.33 ± 10.56	0.663
Sex	**Male**	23 (76.67%)	26 (86.67%)	0.506
	Female	7 (23.33%)	4 (13.33%)	
Cardiac history	**RHD**	8 (26.67%)	0 (0.00%)	**0.002***
	Valve replacement	2 (6.67%)	0 (0.00%)	
IV drug addicts		17 (56.67%)	0 (0.00%)	**<0.001***
Heart rate (beats/min)		102.00 ± 8.20	76.76 ± 7.78	**<0.001***
Systolic blood pressure (mmHg)		107.00 ± 8.80	114.33 ± 13.17	**0.019***
Diastolic blood pressure (mmHg)		68.10 ± 9.28	72.38 ± 7.68	0.111
Respiratory rate	**Normal**	19 (63.33%)	30 (100.00%)	**<0.001***
	High	11 (36.67%)	0 (0.00%)	
Temperature	**Normal**	0 (0.00%)	30 (100.00%)	**<0.001***
	High	30 (100.00%)	0 (0.00%)	
Serum ferritin level		1151.7 ± 470.02	150.67 ± 67.89	**<0.001***

Data are presented as mean ± SD or frequency (%), RDH: Rheumatic heart disease *: statistically significant at P value ≤ 0.05

Table 2 shows ECG findings and laboratory data in group I.

Table 2: ECG findings and laboratory data in group I (n=30)

		Group I (n = 30)
ECG sinus rhythm	**Sinus tachycardia**	27 (90.00%)
	Normal	3 (10%)
Serum creatinine (mg/dL)		1.42 ± 0.47
CRP	**+ve**	30 (100.00%)
	-ve	0 (0.00%)
CBC	**Anemia**	25 (83.33%)
	Leukocytosis	26 (86.67%)
	Thrombocytopenia	2 (6.67%)
	Normal	0 (0.00%)
Blood culture	**Staph**	2 (6.67%)
	Other organisms	26 (86.67%)
	No growth	2 (6.67%)
Virology	**HCV**	17 (56.67%)
	HBV	3 (10.00%)
	HIV	0 (0.00%)
	-ve	13 (43.33%)

Data are presented as frequency (%), CRP: C-reactive protein: CBC: complete blood count

Age, sex, cardiac history, IV drug addicts, heart rate, systolic BP, diastolic BP, respiratory rate and temperature were insignificantly different between both subgroups. Serum ferritin level was significantly increased in subgroup A than subgroup B (P <0.001). Table 3

Table 3: Demographic data, risk factors, vital signs and serum ferritin level of the studied patients

		Subgroup A (N = 19)	Subgroup B (N = 11)	P value
Age (years)		35.32 ± 12.10	35.91 ± 10.61	0.591
Sex	**Male**	13 (68.42%)	6 (54.55%)	0.696
	Female	6 (31.58%)	5 (27.27%)	
Cardiac history	**RHD**	5 (26.32%)	3 (27.27%)	0.383
	Valve replacement	1 (5.26%)	1 (9.09%)	
IV drug addicts		11 (57.89%)	6 (54.55%)	0.859
Heart rate (beats/min)		101.68 ± 8.42	101.73 ± 5.12	0.608
Systolic blood pressure (mmHg)		107.89 ± 14.37	105.45 ± 11.28	0.341
Diastolic blood pressure (mmHg)		68.42 ± 9.58	66.36 ± 6.74	0.277
Respiratory rate (breaths/min)		23.26 ± 5.25	23.09 ± 3.73	0.925
Temperature (°C)		39.28 ± 0.78	39.27 ± 0.52	0.981
Serum ferritin (ng/dL)		1711.84 ± 240.53	879.82 ± 258.84	**<0.001***

Data are presented as mean ± SD or frequency (%), RDH: Rheumatic heart disease *: statistically significant at P value ≤ 0.05

Cyanosis and Clubbing were significantly increased in subgroup A than subgroup B (P <0.001, =0.014 respectively). Chest CT (pneumonia) and abdomen pelvis US (splenic, renal,

liver infarction and mycotic aneurysm) were significantly different between both subgroups (P <0.001). DCL, pallor, brain CT and fundus examination were insignificantly different between both subgroups. Table 4

Table 4: General examination and imaging in subgroup A and B

			Subgroup A (n = 19)	Subgroup B (n=11)	P value
General examination	**DCL**		2 (10.5%)	0 (0%)	0.52
	Cyanosis		16 (84.21%)	0 (0%)	**<0.001***
	Clubbing		8 (42.11%)	0 (0%)	**0.014***
	Pallor		4 (21.05%)	0 (0%)	0.268
Imaging	**Chest CT**	**Normal**	6 (31.58%)	11 (100%)	**<0.001***
		Pneumonia	13 (68.42%)	0 (0%)	
	abdomen pelvis US	**Splenic infarction**	10 (52.63%)	0 (0%)	**<0.001***
		Renal infarction	2 (10.53%)	0 (0%)	
		Liver infarction	4 (21.05%)	0 (0%)	
		Mycotic aneurysm	2 (10.53%)	0 (0.00%)	
		None	1 (5.26%)	11 (100%)	
	Brain CT	**Infarction**	4 (21.05%)	0 (0%)	0.102
		Normal	15 (78.95%)	11 (100%)	
	Fundus examination	**Normal**	16 (84.21%)	8 (81.82%)	0.641
		Roth spots	3 (15.79%)	3 (27.27%)	

Data are presented frequency (%), DCL: Disturbed consciousness level, CT: computed tomography, US: Ultrasound, *: statistically significant at P value ≤ 0.05

Clinical symptoms, Osler nodes and echocardiographic findings were insignificantly different between both subgroups. New murmur, petechiae and splenomegaly were significantly increased in subgroup A than subgroup B (P <0.05). Table 5

Table 5: Clinical manifestations and echocardiographic findings in subgroup A and B

		Subgroup A (n = 19)	Subgroup B (n=11)	P value
Clinical symptoms	**Fever**	19 (100.0%)	10 (90.91%)	0.367
	Cough	11 (57.89%)	6 (54.55%)	0.858
	Dyspnea	13 (68.42%)	7 (63.64%)	0.789
	Hemoptysis	5 (26.32%)	0 (0.00%)	0.129
	Chest pain	4 (21.05%)	0 (0.00%)	0.268
New murmur		14 (73.68%)	0 (0.00%)	<0.001*
Skin	**Petechiae**	14 (73.68%)	0 (0.00%)	<0.001*
	Osler nodes	2 (10.5%)	0 (0.00%)	0.52
Splenomegaly		10 (52.63%)	0 (0.00%)	0.004*
Echocardiographic findings	**Mitral**	5 (26.32%)	4 (36.36%)	0.942
	Aortic	3 (15.79%)	2 (18.18%)	
	Tricuspid	2 (10.53%)	1 (9.09%)	

Data are presented frequency (%), *: statistically significant at P value ≤ 0.05

Complications were insignificantly different between both subgroups. In-hospital outcome was significantly increased in subgroup A than subgroup B (P <0.001). Table 6

Table 6: Complications and Duke's criteria and in-hospital outcome in subgroup A and B

		Subgroup A (n = 19)	Subgroup B (n=11)	P value
Complication	**Congestive HF**	5 (26.32%)	0 (0 %)	0.129
	Kidney damage	4 (21.05%)	0 (0 %)	0.268
	Pulmonary embolism	6 (31.58%)	0 (0 %)	0.061
	Complication related to therapy	3 (15.79%)	0 (0 %)	0.279
	cerebrovascular stroke	6 (31.58%)	0 (0 %)	0.061
	Hemorrhage	5 (26.32%)	0 (0 %)	0.129
Outcome	**Good**	2 (10.53%)	11 (100%)	**<0.001***
	Bad	17 (89.47%)	0 (0%)	

Data are presented frequency (%), *: statistically significant at P value ≤ 0.05

Figure 1 shows that serum ferritin can significantly predict bad outcome (P value<0.001) with AUC of 0.964 (95% CI: 0.881 – 0.995). At cut off >1200, serum ferritin can significantly predict bad outcome with 94.44% sensitivity, 92.86% specificity, 85% PPV and 97.5% NPV.

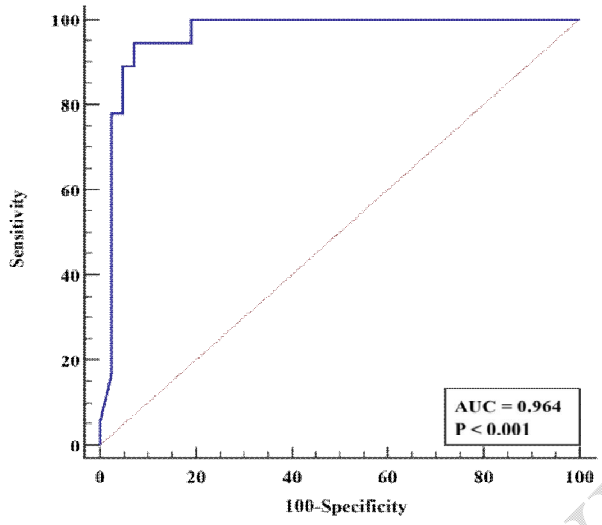

Figure 1: ROC curve of serum ferritin to predict outcome of the studied patients

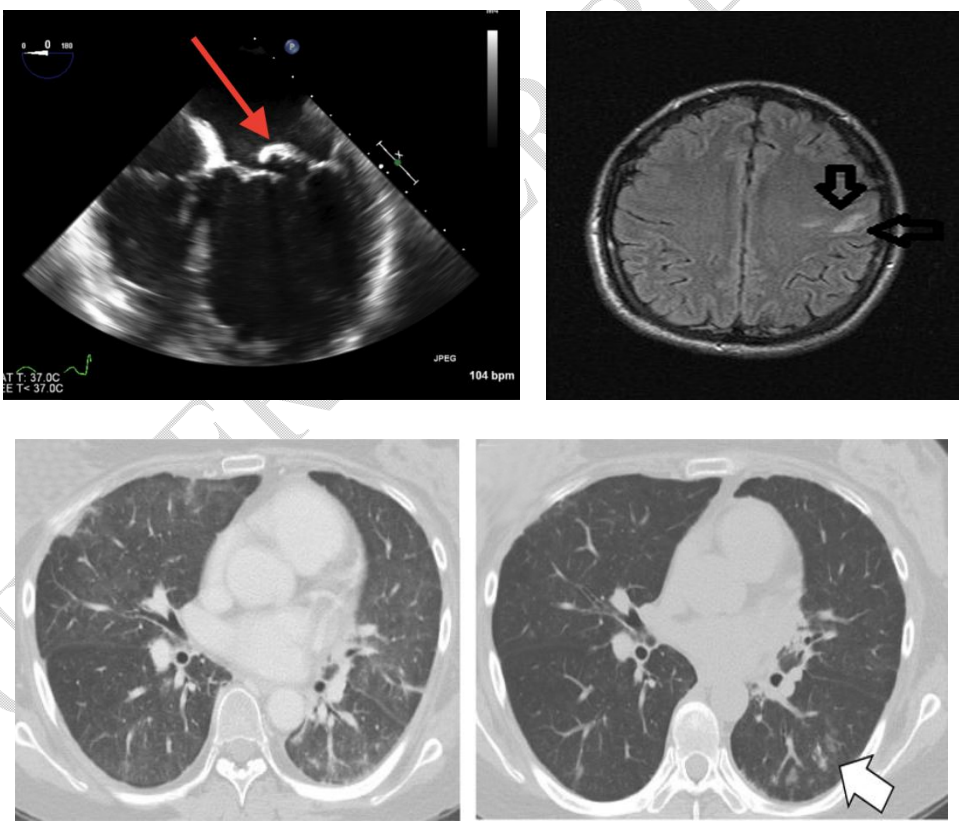

Figure 2: Male patient aged 55 years HTN, not DM, smoker with history of mitral valve prolapse presented with high grade fever 2days before admission. Chest examination shows bilateral crackles. Heard pansystolic murmur at mitral area. Abdominal examination shows splenomegaly. CT chest shows congestion with pneumonic patches. CT brain shows small parietal infarction

Discussion

IE is a non-contagious infection of the lining of the heart valves and heart chambers resulting in infectious organisms such as bacteria and fungi [1].

In the present study, chest CT showed that patients in subgroup A were more prone to pneumonia, US abdomen pelvis demonstrated higher incidence of splenic insult, liver insult in subgroup A compared to subgroup B, but comparable renal affection. Regarding brain CT, subgroup A patients reported recorded higher infarction incidence and similar Roth spots detected by fundus examination. However, overall, imaging was significantly different between both subgroups.

In agreement with the present results, Parra et al. [16] studied 147 IE cases, diagnosed based on Duke criteria and found that male cases with left-sided symptoms On CT, those with liver disease and extra-abdominal emboli were more likely to have abdominal lesions. On abdominal CT scans done on LS-IE cases, the existence of SRL infarcts seems to have little practical relevance.

Inflammation is associated with serum ferritin, which might be elevated in the context of chronic inflammation. During chronic inflammation, the body manufactures hepcidin in the liver to prevent pathogens from utilizing serum iron by inhibiting intestinal absorption and sequestration of iron in the macrophage, resulting in a comparatively iron-deficient condition that is represented by an increase in serum ferritin [17, 18]. This could explain the results in the present study; all patients in subgroup A who reported cardiac events had serum ferritin >1200 ng/dL while patients in subgroup B who showed no cardiac events had serum ferritin 400-1200 ng/dL.

In accordance with the current study, Petrova et al.[19] studied indicators of systemic inflammatory response in IE cases and observed that their ferritin levels were high upon admission. Ferritin levels rose on day 1 postoperatively, continued to rise on day 3, when

they reached their peak, and began to decline on day 6. To conclude based on this data that ferritin level may be utilized to characterise postoperative circumstances, including systemic inflammatory symptoms and surgical treatment finding.

In the present study, subgroup A patients were more prone to symptoms as fever, cough, dyspnea, hemoptysis chest pain than patients in subgroup B. Also, new murmur was highly frequent in subgroup A than subgroup B. Patients with cardiac events suffered more from kin manifestations as petechiae yet were comparable in Osler nodes. Splenomegaly was detected more frequently among subgroup A patients.

In their study, Servy et al. [20] reported that 487 out of 497 patients had known dermatological manifestations and the most common manifestations, included purpura (8%). It was also found that cases having skin symptoms had an elevated rate of IE-related extracardiac difficulties, but with no increase in the mortality rate. In our research, petechiae was the main dermal manifestation and it affected most of patients.

ECHO is preferable for visualising cardiac symptoms caused by IE [21]. In our research, by utilizing Echo findings, we detected mitral vegetations, aortic vegetations and tricuspid vegetations in subgroup Abut no defects occurred in subgroup B.

Compatible with present results, Damlin et al. [21] examined relationships among bacterial illnesses and ECHO-diagnosed IE symptoms. Data from cases with 18 years and older with confirmed IE were gathered. ECHO-diagnosed IE manifestations were acquired from the registry. Their results highlighted that mitral vegetation 195 (40%), aortic vegetation 190 (39%), and tricuspid vegetation 108 (22%) were the most frequent signs.

Variables such as the infecting pathogen, length of sickness prior to therapy, and kind of treatment influence the prevalence of certain consequences [22]. We observed that congestive HF, kidney damage, pulmonary embolism, complication related to therapy, cerebrovascular stroke, hemorrhage demonstrated higher incidence in subgroup A patients. Further, all

patients from both groups with endocarditis fulfilled duke's criteria. Generally, complications were insignificantly different between both subgroups.

Moreover, Spelman et al.[23] reviewed 223 episodes of IE, 57% of cases had one difficulty, 26% had two, 8% had three, 6% had four, 1% had five, and 1% had six or more difficulties. IE consequences include cardiac, musculoskeletal, renal, neurologic, and pulmonary troubles, in addition to systemic infection consequences as metastatic infection, embolization, and mycotic aneurysm. Multiple complications may develop concurrently.

According to our findings, as subgroup A suffered from more complications, so it was expected that outcomes were significantly worse in subgroup A compared to subgroup B (P value<0.001**)**.

Similarly, in their study, Nunes et al. [24]conducted a study on two hundred and three patients with IE. They found that heart failure and periannular outcomes are well-established negative prognostic indicators. Cases who had surgery may have been safeguarded against a worsening of their condition.

In the present study, serum ferritin can significantly predict bad outcome (P value<0.001) with AUC of 0.953 (95% CI: 77.4 – 97.3). At cut off >1200, serum ferritin can significantly predict bad outcome with 94.44% sensitivity, 90.48% specificity, 81% PPV and 97.4% NPV.

In similarly study Van der Meer et al. [25] reported that serum ferritin was a potential predictor of 10-year hard CHD.

Limitations: Sample size was relatively small; more trials need to be conducted to verify the findings of our study and the study was at only one center.

Conclusions:

Serum ferritin was significantly increased in IE subjects who experienced problems on admission as compared to IE subjects who didn't.

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