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Research Article

"Study Of Serum Iron Levels as A Prognostic Marker in Sepsis in Adults"

Srinivas G[1*], Mahesh S Kanth[2], Savesh Roshan[3], Naval Kishor[4]

[1]Srinivas G, Associate Professor, Department of General Medicine, Bangalore Medical College and Research Institute
[2]Mahesh S Kanth, Post graduate, Department of General Medicine, Bangalore Medical College and Research Institute
[3]Savesh Roshan, Assistant professor, Department of General Medicine, Bangalore Medical College and Research Institute
[4]Naval Kishor, Post graduate, Department of General Medicine, Bangalore Medical College and Research Institute

ABSTRACT

Title : Study of serum iron levels as a prognostic marker in sepsis in adults - prospective cohort study

Background: Sepsis is a life-threatening condition with high mortality rates among critically ill patients. Understanding the role of biomarkers, such as serum iron levels, in predicting the prognosis of sepsis can enhance patient management and outcomes.

Objectives: The objectives of this study was to evaluate serum iron levels as a prognostic marker in adult patients with sepsis, assessing the relationship between S.iron profile (T-sat and S.ferritin) and clinical outcomes, as well as their correlation with SOFA and APACHE II scores.

Methods: This prospective cohort study was conducted at BMCRI. 90 Adult patients diagnosed with sepsis or septic shock were enrolled and their S.iron levels were measured. Additional parameters such as transferrin saturation and serum ferritin were also recorded. Clinical outcomes were tracked, and correlations with SOFA and APACHE II scores were analyzed.

Results: Most patients are in the 51-60 years age range (21.3%), with males (55%) compared to females (45%). The most common organism isolated among the patients was A.baumanii (42.5%). The study found that S.iron levels were significantly lower in non-survivors (<50 mcg/L in 81.5% of patients, p=0.004) compared to survivors (>50 mcg/L in 53.8% of patients) of sepsis. Lower serum iron levels and T-sat, and higher ferritin were associated with higher SOFA and APACHE II scores, indicating more severe organ dysfunction and higher mortality risk.

Conclusion: Serum iron levels can serve as a prognostic marker in sepsis, with lower levels indicating poorer outcomes. Monitoring serum iron and related parameters could aid in the early identification of high-risk patients and improve clinical decision-making.

Keywords: Sepsis, Serum Iron Levels, Prognostic Marker, SOFA Score, APACHE II Score, Transferrin Saturation, Serum Ferritin

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INTRODUCTION

Sepsis, a severe and life-threatening condition, has the highest mortality rate among critically ill patients. The World Health Organization's latest estimates for 2017 indicate that 48.9 million people were affected by sepsis, resulting in 11 million deaths worldwide, which

constitutes approximately 20% of all global deaths. Low- and middle-income countries accounted for about 85% of sepsis cases and sepsis-related deaths, highlighting significant regional disparities[1]. Although over two-thirds of patients survive sepsis, one-third die within the first year, and 40% are readmitted to the hospital within the first 90 days after discharge[2].

According to survival sepsis guidelines, sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection. It is one of the most common causes of intensive care unit (ICU) admissions worldwide. Septic shock is a severe subset of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities that present a higher mortality risk compared to sepsis alone. Clinically, septic shock is identified by the need for vasopressors to maintain a mean arterial pressure of 65 mmHg or a serum lactate level exceeding 2 mmol/L (18 mg/dL), provided there is no hypovolemia. This condition is associated with hospital mortality rates exceeding 40%[3]. High-risk groups include neonates, pregnant women, older adults, hospitalized patients, those in intensive care units, and individuals with chronic diseases or comorbidities[4].

The clinical signs and symptoms of sepsis typically include fever or low body temperature, shortness of breath, altered mental status, tachycardia, tachypnea, hypotension, and cyanotic or mottled skin[5].

Trace elements are abundant in the human body, with iron being one of the most prevalent. Numerous studies have highlighted the significant role of trace elements in various diseases[6]. Iron is a crucial nutrient involved in several physiological processes, such as hemoglobin synthesis, oxygen transport, energy production, and immune function[7]. During sepsis, the body's response to infection can disrupt iron metabolism, leading to increased iron sequestration and reduced availability for erythropoiesis and other essential functions. This alteration in iron metabolism is believed to be a defensive response to pathogens, as iron is vital for bacterial growth and proliferation. However, excessive iron sequestration in sepsis can also contribute to anemia, impaired immune function, and a higher risk of secondary infections[8]. Monitoring iron levels in sepsis patients, particularly through transferrin saturation and ferritin measurements, can offer valuable insights for risk assessment and management of sepsis-related complications. Additionally, interventions aimed at modifying iron metabolism, such as iron supplementation or chelation, may offer potential therapeutic strategies in managing sepsis.

Indicators of iron status include serum iron, serum ferritin, total iron-binding capacity, serum transferrin, and transferrin saturation. Transferrin saturation (TSAT) measures the proportion of iron bound to transferrin, the protein responsible for iron transport in the blood. It is calculated as the ratio of serum iron to total iron-binding capacity, expressed as a percentage. TSAT levels are typically decreased in conditions such as iron deficiency anemia and chronic inflammation, while they are elevated in cases of iron overload. In sepsis, TSAT levels often decrease due to inflammation-induced iron sequestration and diminished erythropoiesis[9].

Serum ferritin is a useful marker of total iron stores. During sepsis, ferritin levels may rise because pro-inflammatory cytokines stimulate ferritin production, leading to increased iron sequestration as part of the body's defense against pathogens. However, elevated ferritin in sepsis may also reflect a dysregulation of iron metabolism and inflammation, and can be associated with poorer clinical outcomes[10]. Despite the recognized importance of iron metabolism in various bodily functions, its role in sepsis is not fully understood. This study aims to explore the role of different iron-related markers and their potential as early indicators for assessing the severity and mortality of sepsis and septic shock patients.

OBJECTIVES

- To estimate serum iron levels in patients with sepsis and septic shock.
- To clinically correlate serum iron levels with outcome in patients with sepsis.
- To correlate the levels of other serum Iron profile levels like transferrin saturation and serum ferritin in patients with severe sepsis and septic shock with the Sequential [Sepsis-related] Organ Failure Assessment(SOFA) and APACHE II (Acute Physiology and Chronic Health Evaluation II) Scores

MATERIALS AND METHODS

Source of data:

All patients with sepsis and septic shock defined based on survival sepsis campaign guidelines admitted at medical intensive care unit

A. Study design: cross sectional study

B. Study period : August 2022 to January 2024

C. Place of study : Hospitals attached to Bangalore Medical College and Research Institute.

D. Study sample size: 70

Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Z : Standard table value for 95% confidence interval(CI)i.e.,1.96
n: Number of sample size.
Where, p = 0.3278, d = 11% , 1-a=95%
On substituting values
n= [1.96²X0.3278(1-0.3278)]/0.11²
n=70

E. Inclusion Criteria:
All consenting patients who are more than 18 years of both sexes admitted in Intensive Care Unit (ICU) with features of sepsis or septic shock defined by survival sepsis guidelines.

F. Exclusion Criteria:
1. Blood transfusion or iron supplementation in the last 90 days, previous inclusion.
2. Pregnant and lactating mothers.
3. Post cardiopulmonary resuscitated patient.
4. Patients with iron deficiency anemia.
5. Malabsorption syndromes.
6. Patients with chronic diarrhea.
7. Patients with chronic kidney disease.

Methodology
A cross sectional study will be conducted at the medical allied intensive care unit, the department of General medicine in a tertiary care hospital, Bangalore medical College and research institute, Bangalore. After obtaining approval and ethical clearance from the institutional ethics committee of Bangalore medical college and research institute(BMCRI), Bangalore 70 patients fulfilling the inclusion criteria will be enrolled for the study after obtaining informed consent.
The study collected and analyzed various information for each patient, including demographics, volume resuscitation, vasopressor requirement, and organ failure. Haematological and biochemical data were measured, and routine blood cultures and cultures from infection sites were performed. Disease severity was assessed using Sepsis-related Organ Failure Assessment (SOFA) scores and APACHE-II scores on the day of ICU admission, 24 hours after admission, and subsequent assessments until 28 days or mortality. Blood samples were collected at admission to measure Serum Iron, Ferritin, and Transferrin saturation levels. Specific levels were defined, such as Iron level (50-150 mcg/L), Ferritin level (22-336 ng/ml) and TSAT level (25-50%). Patients received standard treatment for sepsis and septic shock according to surviving sepsis-3 guidelines.
Follow-up of patients continued for 28 days or until death, whichever occurred earlier. The levels were correlated with the outcome and compared with the prognostic scoring system of sepsis, such as APACHE II and SOFA scores. Blood samples were taken specifically for the study purposes, aiding in the diagnosis and improved management of conditions like Iron deficiency anaemia in critical care patients. The investigator covered the cost of these blood investigations.

STATISTICAL ANALYSIS
SPSS (Statistical Package For Social Sciences) version 21. (IBM SPASS statistics [IBM corporation: NY, USA]) was used to perform the statistical analysis
- Data was entered in the excel spread sheet.
- Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.
- Inferential statistics like

o Chi-square test was applied for qualitative variables to find the association.
o Independent sample t test was applied to compare the quantitative parameters between the groups
- The level of significance is set at 5%.

RESULTS

TABLE 1: MEAN AGE DISTRIBUTION OF THE SUBJECTS

	N	Minimum	Maximum	Mean	S.D
Age	80	18.0	86.0	51.26	18.72

INFERENCE: The mean age of the patients was 51.26 ± 18.72 years.

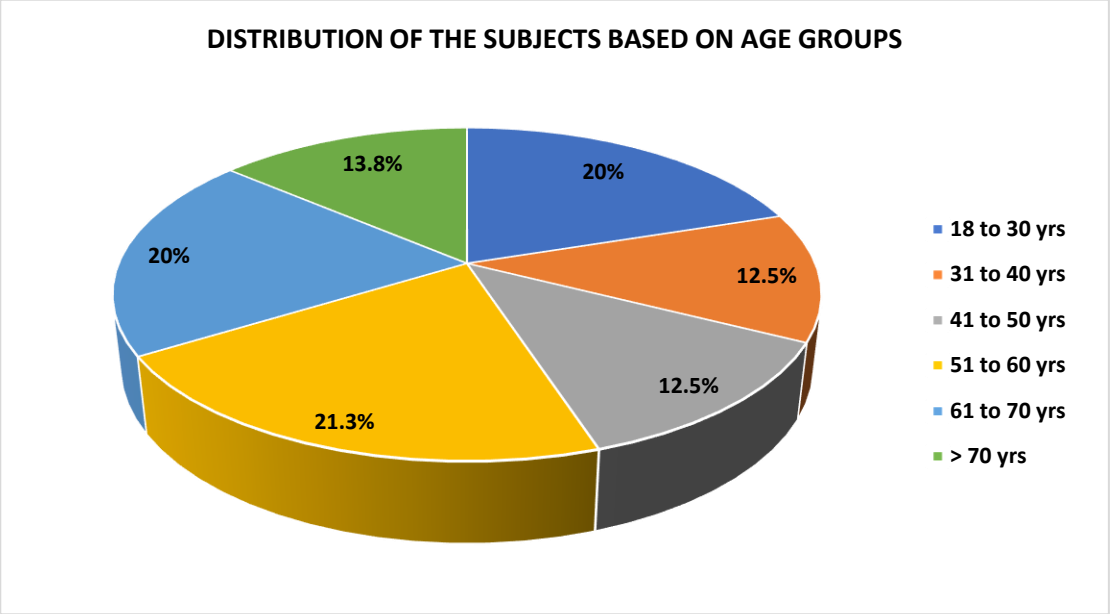
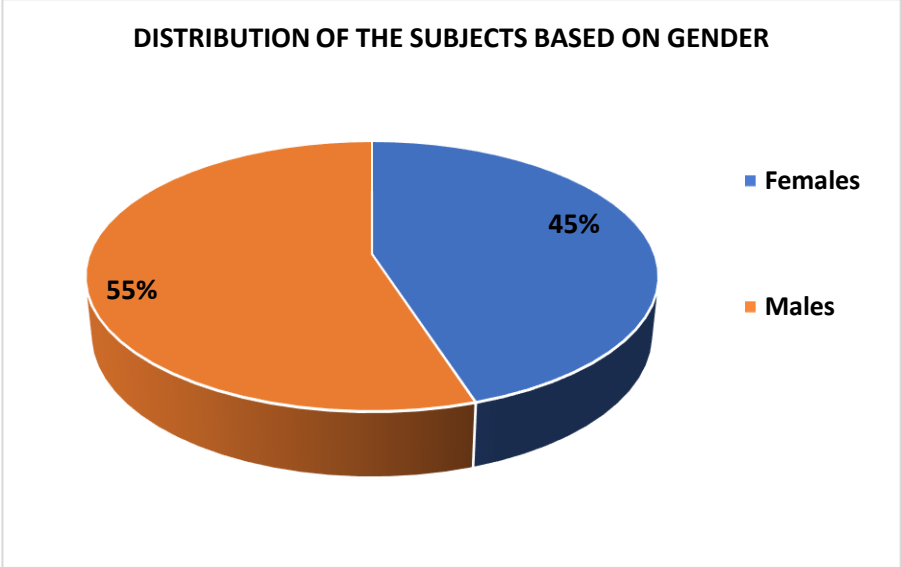


Figure 1 : Distribution of the subjects based on age groups

Figure 2 : Distribution of the subjects based on gender.



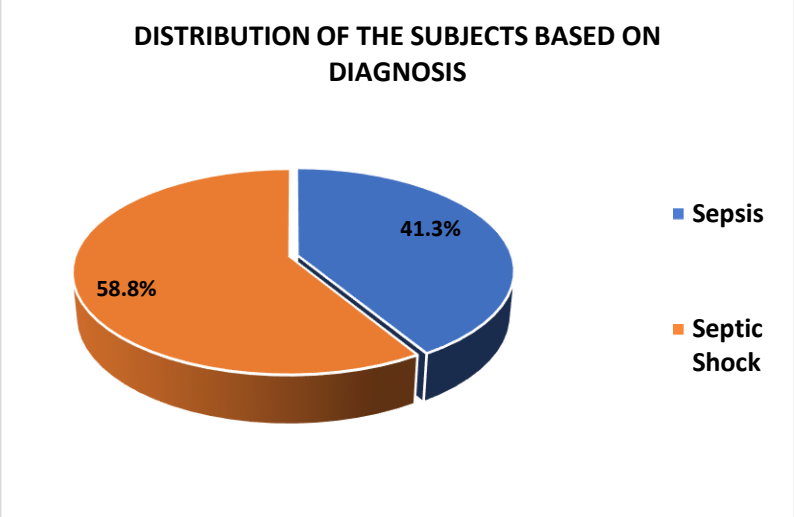


Figure 3 : Distribution of the subjects based on diagnosis

INFERENCE: 33 patients (41.3%) were diagnosed with sepsis and 47 patients (58.8%) were diagnosed with septic shock.

TABLE 2: DISTRIBUTION OF THE SUBJECTS BASED ON SOURCE OF INFECTION

Source of Infection	Frequency	Percent
Respiratory	72	90.0
Genitourinary	10	12.5
Gastrointestinal	6	7.5
Central nervous system	8	10.0
Skin and soft tissue	12	15.0
CRBSI	5	6.3
Bacteraemia	5	6.3

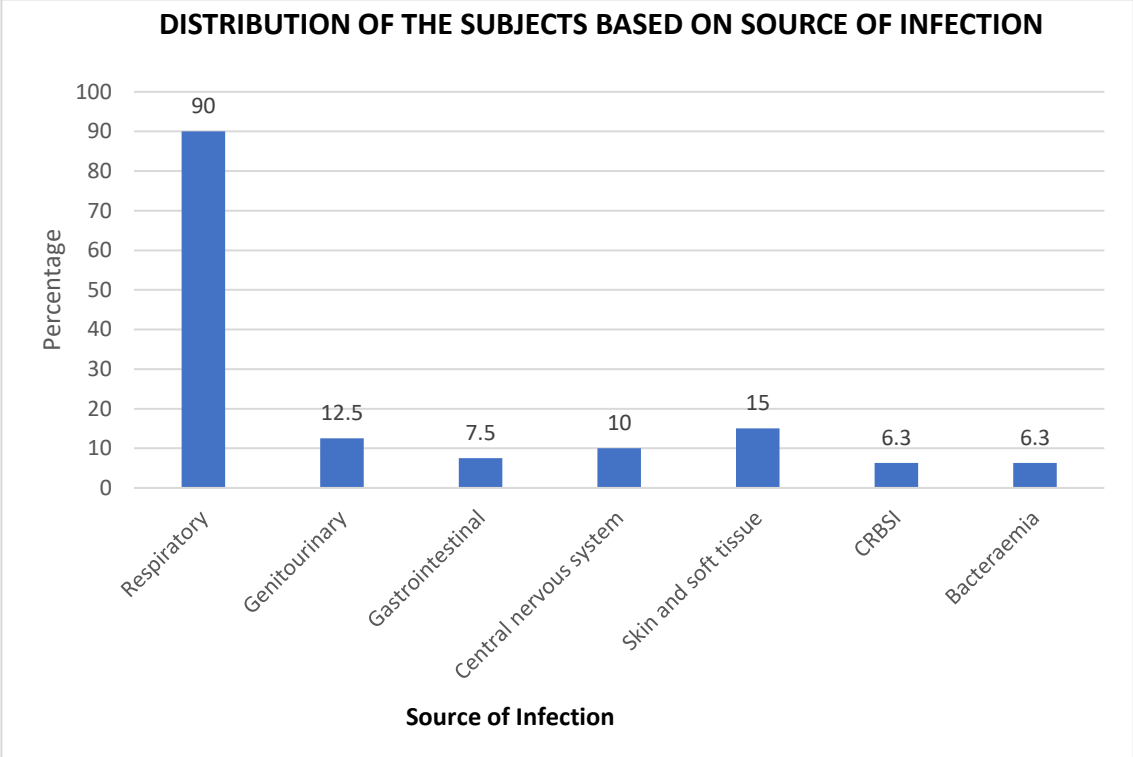


Figure 4 : Distribution of the subjects based on source of infection.

TABLE 3: DISTRIBUTION OF THE SUBJECTS BASED ON MICROORGANISM

Microorganism	Frequency	Percent
Acinetobacter Baumanni	34	42.5
Pseudomonas aeruginosa	13	16.3
Klebsiella pneumonia	24	30.0
MRSA	10	12.5
Escheria coli	4	5.0
Candida	2	2.5

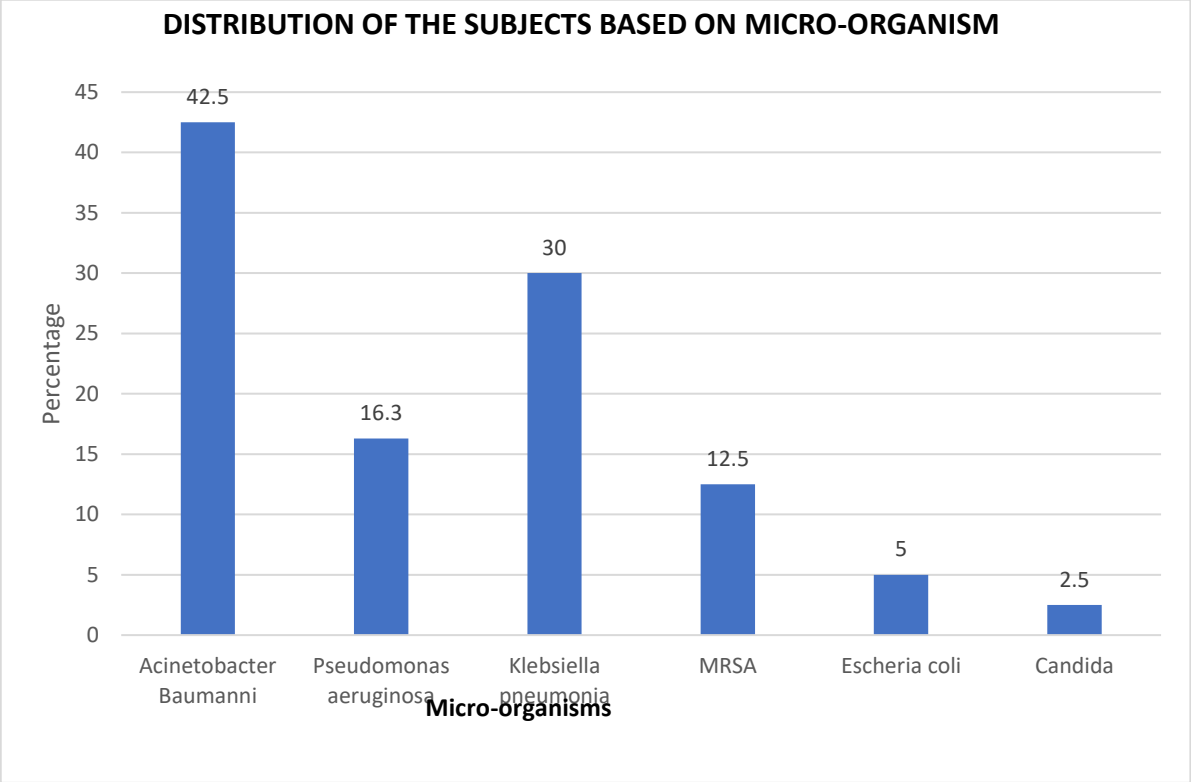


Figure 5 : Distribution of the subjects based on microorganisms.

TABLE 4: DISTRIBUTION OF THE SUBJECTS BASED ON CO-MORBIDITIES

Co-morbidities	Frequency	Percent
Diabetes	32	40.0
Hypertension	27	33.8
CAD	15	18.8
Liver Disease	12	15.0
Neurological disease	13	16.3
Thyroid disorder	5	6.3
Respiratory disorder	13	16.3
Malignancy	1	1.3
Autoimmune disorder	3	3.8

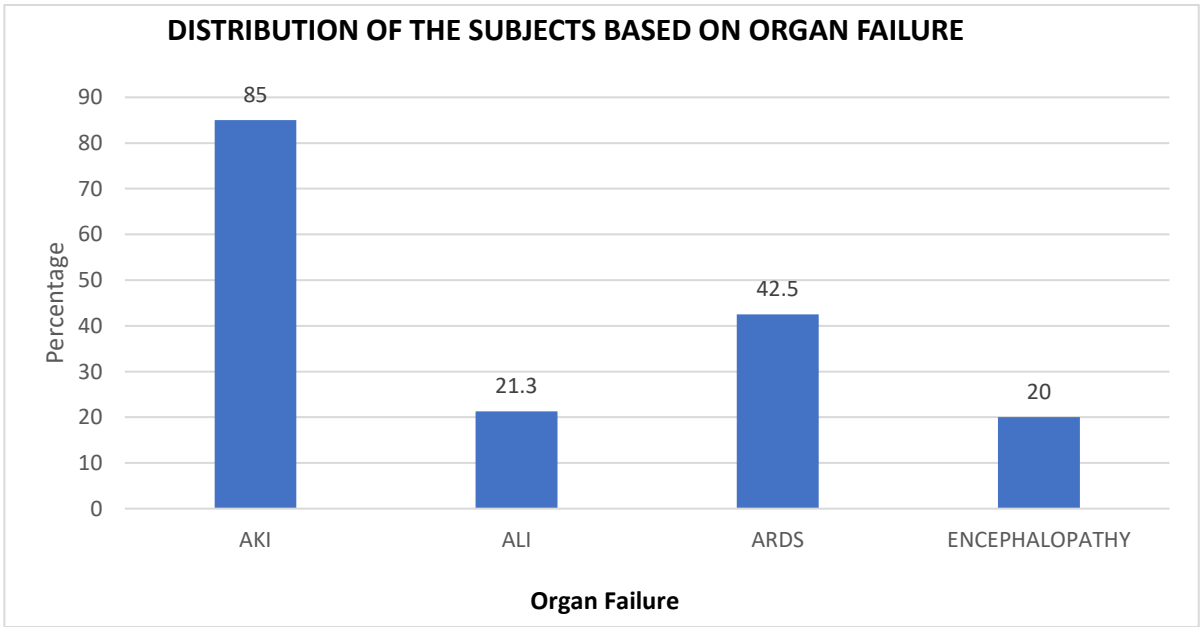


Figure 6 : Distribution of the subjects based on organ failure.

TABLE 5: ASSOCIATION OF IRON AND OUTCOME

Iron		Outcome		Total
		Survived	Mortality	
< 50	Count	12	44	56
	%	46.2%	81.5%	70.0%
50 to 150	Count	13	10	23
	%	50.0%	18.5%	28.7%
>150	Count	1	0	1
	%	3.8%	0.0%	1.3%
Total	Count	26	54	80
	%	100.0%	100.0%	100.0%
Chi-square value-11.25				
p value-0.004*				

*significant

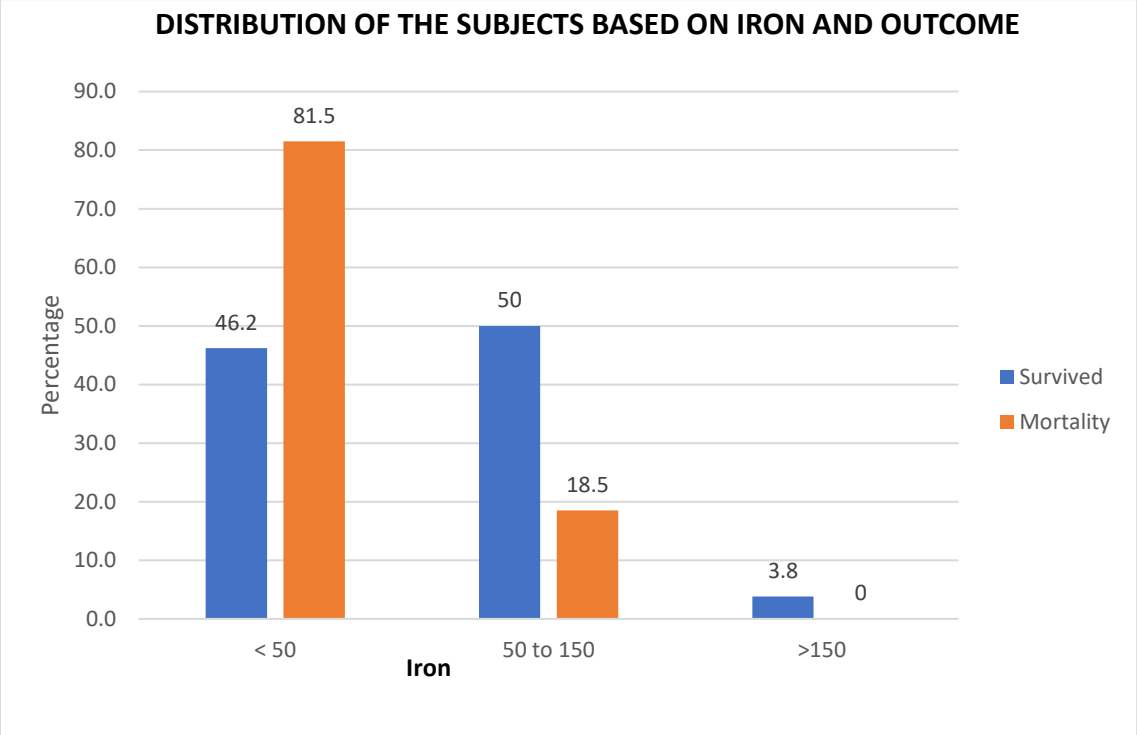


Figure 7 : Distribution of the subjects based on iron and outcome.

TABLE 6: ASSOCIATION OF FERRITIN AND OUTCOME

Ferritin		Outcome		Total
		Survived	Mortality	
< 22	Count	0	1	1
	%	0.0%	1.9%	1.3%
22 to 336	Count	14	5	19
	%	53.8%	9.3%	23.8%
>336	Count	12	48	60
	%	46.2%	88.9%	75.0%
Total	Count	26	54	80
	%	100.0%	100.0%	100.0%
Chi-square value-19.44				
p value-0.002*				

*significant

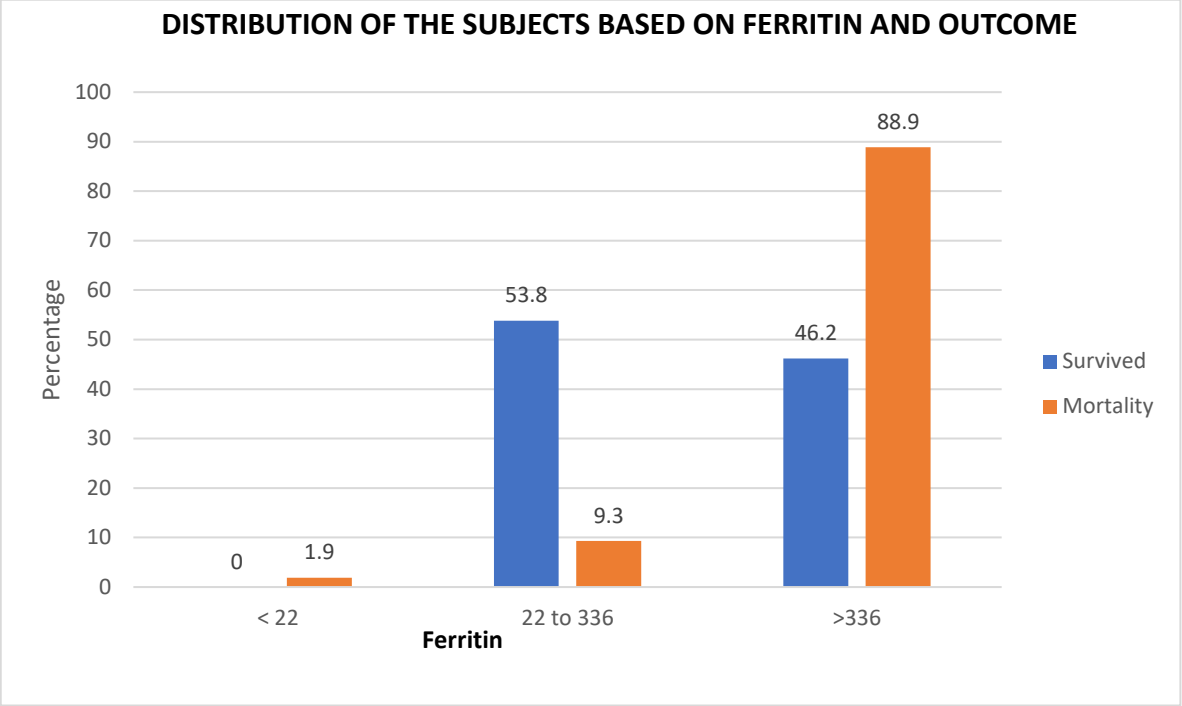


Figure 8 : Distribution of the subjects based on Ferritin and outcome.

TABLE 7: ASSOCIATION OF TRANSFERRIN SATURATION AND OUTCOME

T Saturation		Outcome		Total
		Survived	Mortality	
< 25	Count	2	39	41
	%	7.7%	72.2%	51.2%
25 to 50	Count	23	15	38
	%	88.5%	27.8%	47.5%
>50	Count	1	0	1
	%	3.8%	0.0%	1.3%
Total	Count	26	54	80
	%	100.0%	100.0%	100.0%
Chi-square value- 29.94				
p value-0.002*				

*significant

TABLE 8: COMPARISON OF THE SOFA SCORE BASED ON OUTCOME USING INDEPENDENT SAMPLE T TEST

Outcome	N	Minimum	Maximum	Mean	S.D	Mean diff	p value
Survived	26	5.0	10.0	6.31	1.19	-5.15	0.001*
Mortality	54	2.0	16.0	11.46	3.35		

*significant

TABLE 9: COMPARISON OF THE APACHE II SCORES BASED ON OUTCOME USING INDEPENDENT SAMPLE T TEST

Outcome	N	Minimum	Maximum	Mean	S.D	Mean diff	p value
Survived	26	8.0	30.0	15.04	5.06	-15.50	0.001*
Mortality	53	12.0	40.0	30.55	8.05		

*significant

TABLE 10: ASSOCIATION OF DIAGNOSIS AND IRON

Iron		Outcome		Total
		Survived	Mortality	
Abnormal	Count	13	44	57
	%	50.0%	81.5%	71.3%
Normal	Count	13	10	23
	%	50.0%	18.5%	28.7%
Total	Count	26	54	80
	%	100.0%	100.0%	100.0%
Chi-square value- 8.49				
p value-0.004*				
Odd's Ratio- 0.227				
OR 95% CI- 0.081 to 0.637				

*significant

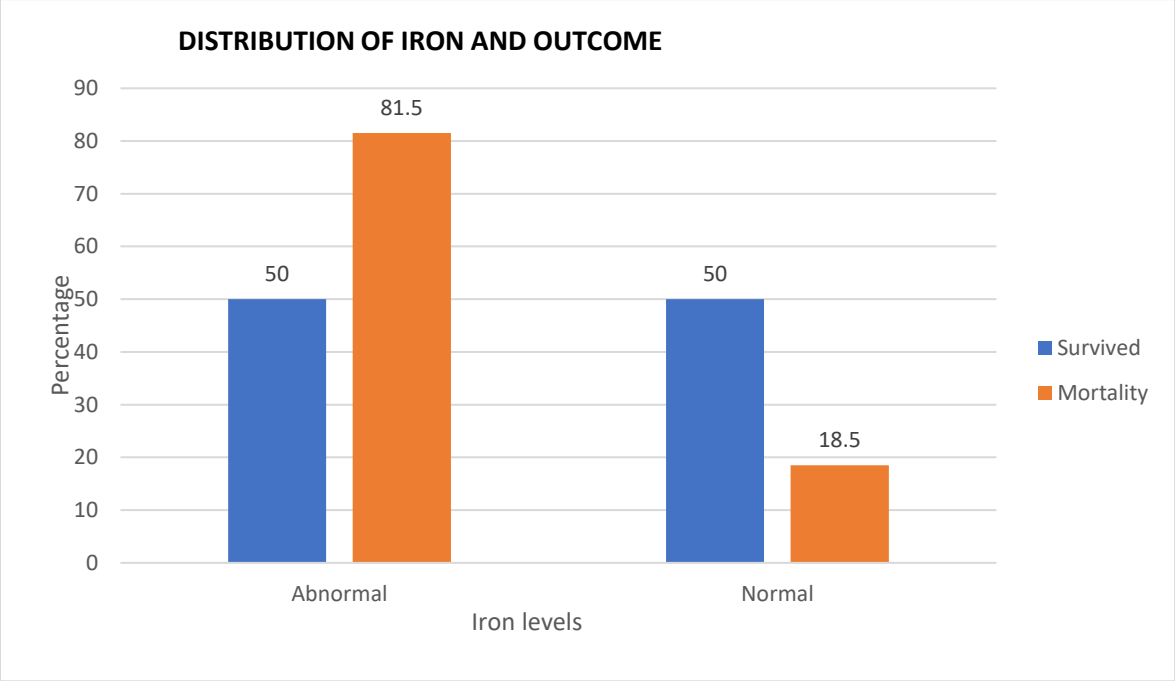


Figure 9 :Distribution of iron and outcome

DISCUSSION

Given that iron is a vital component of many physiological metabolic processes and is a necessary nutrient for bacteria, iron plays a crucial role during infection. So, in order for the bacteria to grow rapidly during an infection, the host and the bacteria must compete for iron. The majority of iron in the human body is stored by hemoglobin.[11] Iron is simultaneously retained by the body through the combined actions of complement proteins, iron-binding proteins, and antibodies. However, bacteria may also absorb iron that is attached to proteins via a variety of pathways, including siderophores, which are released by pathogens and have a greater affinity for iron than host transport proteins.[12] Furthermore, reactive oxygen species are produced when free iron contributes or absorbs electrons with ease, making it hazardous.[13] Iron chelators have the potential to reverse the infection susceptibility associated with hemochromatosis, a genetic iron overload disorder. As a result, infections may arise from elevated iron levels.[14] The objective of this research was to determine the serum iron levels in individuals diagnosed with sepsis.

Age

Elderly patients with sepsis are at high risk for severe complications and are frequently admitted to the intensive care unit (ICU).[15] In this study, the average age of patients was 51.26 ± 18.72 years, with the majority (21.3%) aged between 51 and 60 years. However, no statistically significant association was found between age group and outcome (p=0.30). These results align with findings from Lan P et al., which showed that 65.8% of participants were older than 60, while 30.7% were between 31 and 59.[16] Similarly, Brandtner A et al. reported a mean age of 63 years.[17] Older adults, particularly those in nursing homes, experience higher rates of ICU admissions, longer hospital stays, and increased mortality compared to younger individuals.[18] Aging is associated with diminished humoral and cellular immune responses, leading to a compromised immune system. Elderly patients with sepsis exhibit a distinct cytokine release

pattern, with elevated levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α.[19]

Gender

According to Offner et al., the occurrence of serious infection in surgical patients may be independently attributed to the gender of the patient.[20] Males had a noticeably greater rate of bacteremic infections than females, according to McGowan et al.[21]

Based on diagnosis

Sepsis and septic shock, with their high pathophysiological, molecular, genetic, and clinical complexity, are both on the rise globally and provide a challenge to emergency doctors.[22] In the current investigation, sepsis was detected in 33 patients (41.3%) and septic shock in 47 patients (58.8%). Twenty patients (76.9%) and six patients (23.1%) with a diagnoses of sepsis and septic shock, respectively, were among the 26 survivors. In 54 patients who died, 13 patients (24.1%) had a diagnosis of sepsis and 41 patients (75.9%) had a diagnosis of septic shock. In the current investigation, there was a statistically significant correlation between the diagnosis and the result. ($p = 0.001$) On the other hand, 324 (17.1%) of the 1,891 patients with sepsis who met the Sepsis-3 criteria were in septic shock, according to Lan P's observations.[16]

Source of infection

72 patients (90%), genitourinary in 10 patients (12.5%), gastrointestinal in 6 patients (7.5%), central nervous system in 8 patients (10%), skin and soft tissue in 12 patients (15%), CRBSI in 5 patients (6.3%), and bacteraemia in 5 patients (6.3%), were the sources of infection in the current study. Similar to this, Lan P observed that the bulk of infections were caused by respiratory (55.6%), circulatory (43.9%), and urine (39.2%) infections.[16] Similarly, Brandtner et al observed that pneumonia was the predominant main cause of infection in 37.7% of patients, with urinary tract infections accounting for 12.8%. 31.2% of patients died in ICUs.[17]

Organism isolated

Bacterial pathogens encounter a harsh environment in host tissues. In order to ensure their survival, development, and proliferation, bacteria have developed many adaptation strategies. These include the ability to produce a thick capsule, create biofilms, and transform into the L-form.[23] The current investigation identified Acinetobacter Baumanni in 34 patients (42.5%), Pseudomonas aeruginosa in 13 patients (16.3%), Klebsiella pneumonia in 24 patients (30%), MRSA in 10 patients (12.5%), E.coli in 4 patients (5%), and Candida in 2 patients (2.5%). According to Lan P, the two most common infections were Escherichia coli (10.3%) and Staphylococcus (40.3%).[16]

Comorbidities

Comorbidities have a substantial role in mortality in a considerable fraction of patients treated for sepsis in the medical ICU, and sepsis-related deaths without relevant comorbidities are uncommon.[24] Out of the total number of patients in this study, 32 (40%) had diabetes, 27 (33.8%) had hypertension, 15 (18.8%) had CAD, 12 (15%) had liver disease, 13 (16.3%) had neurological disease, 5 (6.3%) had thyroid disorder, 13 (16.3%) had respiratory disorder, 1 (1.3%) had malignancy, and 3 (3.8%) had autoimmune disorder. Yet, according to Lan P et al, 38.6% of the population had hypertension, followed by DM in 31.3% and CHF in 36.7%.[16]

Organ failure.

Organ dysfunction results from a dysregulated immunological response to an infection, which is known as sepsis. Understanding the biology of organ failure in sepsis is essential for improving patient care and therapy as well as for the creation of novel therapeutic approaches. In the present study, based on organ failure, 68 patients (85%) had AKI, 17 patients (21.3%) had ALI, 34 patients (42.5%) had ARDS and 16 patients (20%) had encephalopathy. These results were consistent with those of Bouza et al., who found that 25% of individuals had multiple organ failure and 45% of cases had single organ dysfunction.[25]

The association between iron and result

In patients who survived, 12 patients (46.2%) had iron <50, 11 patients (42.3%) had iron between 50 to 100 and 3 patients (11.5%) had iron >100. In patients who died, 44 patients (81.5%) had iron <50, 5 patients (9.3%) had iron between 50 to 100 and 5 patients (9.3%) had iron >100. The association of iron levels and outcome was statistically significant in the present study ($p = 0.002$). This is according to the study conducted by Xia J et al which showed low serum iron correlated with increased mortality in sepsis patients.[26] In contradiction, Lan P et colleagues found that in sepsis patients, a higher serum iron quartile was linked to a greater 90-day death rate.[16] Conversely, Brandtner et al. found that when patients were categorized based on the infection source, there were no variations in the distribution of iron parameters.[17]

Serum ferritin

Inflammation and iron accumulation in tissues are both indicated by elevated serum ferritin. Ferritin is expressed by all nucleated cell types in order to store iron.[27] Ferritin is necessary in cells to prevent the production of reactive oxygen species, which is caused by iron and causes cellular toxicity, as well as to restrict bacteria' access to iron.[28] Macrophages are thought to be the primary source of serum ferritin due to their strong potential to either produce ferritin via non-classical routes or store iron in ferritin.[29] Therefore, rather than indicating higher iron reserves, the elevated serum ferritin levels seen in non-survivors may indicate enhanced macrophage activity. In patients who survived, 14 patients (53.8%) had ferritin between 22 to 336 and 12 patients (46.2%) had ferritin >336. In patients who died, 1 patient (1.9%) had ferritin <22, 5 patients (9.3%) had ferritin between 22

to 336 and 60 patients (75%) had ferritin >336. The association of ferritin levels and outcome was statistically significant in the present study. (p = 0.002) Ferritin, however, did not seem to have an effect on sepsis survivorship, according to Lan P et al.[16]

T saturation

In the present study, in patients who survived, 2 patients (7.7%) had T saturation <25, 23 patients (88.5%) had T saturation between 25 to 50 and 1 patient (3.8%) had T saturation >50. In patients who died, 39 patients (72.2%) had T saturation <25, 15 patients (27.8%) had T saturation between 25 to 50. The association of T saturation and outcome was statistically significant in the present study. (p = 0.002) These results were consistent with a research by Lan P et al. showing a correlation between sepsis-related mortality and elevated serum ferritin, TF-Sat, and iron levels.[16]

SOFA Score

The sepsis syndrome is currently recognized by a shift in the SOFA score of two or higher.[30] In the present study, the mean SOFA score in patients who survived was 6.31 ± 1.19 and in mean SOFA score in patients who died was 11.46 ± 3.35. The association of SOFA score and outcome was statistically significant in the present study. Similar to Lan P et al., who reported an average SOFA score of 5, ranging from 3 to 8, (p=0.001).[16]

APACHE II

A variety of laboratory results and patient indicators, accounting for both acute and chronic illness, are used by the Apache II Score to predict ICU mortality. The mean APACHE II score in patients who survived was 15.04 ± 5.06 and in mean APACHE II score in patients who died was 30.55 ± 8.05. In the current investigation, there was a statistically significant correlation between the APACHE II score and the result. (p = 0.001) The average APACHE II score, according to Sadaka F et al., was 19 ± 7.[31]

LIMITATIONS

1. Small sample size
2. Single centre study leading to generalisability of the results

CONCLUSION

Increased ferritin and low serum iron concentrations upon ICU admission were shown to positively correlate with both mortality and the SOFA score and APACHE II score. Furthermore, lower transferrin concentrations and higher TF-Sat concentrations were linked to more difficult survival. Additionally, high Sequential [Sepsis-related] Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were significantly associated with increased mortality.

The study reveals interactions—which may be related to iron-mediated effects on microbial growth, immunological function, and/or radical formation—between systemic iron homeostasis and the clinical course of sepsis that were previously overlooked.

However, it is important to consider the limitations of this study, single-center setting, and potential confounding factors. The findings may not be generalizable to other populations or healthcare settings. Further research with larger sample sizes, longitudinal designs, and consideration of potential confounders is needed to confirm these associations and establish causality.

Nonetheless, the results of this study contribute to our understanding of the relationship between iron profile and the outcome in patients with sepsis and septic shock. These findings may have implications for the management and prognostication of patients with sepsis and septic shock, and further exploration of these variables in future research is warranted.

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan;395(10219):200–11.
2. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. JAMA. 2018 Jan 2;319(1):62. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–10.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International ConsensusDefinitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–10.
4. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016 May 23;i1585.
5. Hotchkiss RS, Moldawer LL, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primer. 2016 Jun 30;2:16045.
6. Dharmalingam K, Birdi A, Yadav D, et al. Trace Elements as Immunoregulators in SARS-CoV-2 and Other Viral Infections. Indian J Clin Biochem IJCB. 2021 Oct;36(4):416–26.
7. Ganz T. Systemic iron homeostasis. Physiol Rev. 2013 Oct;93(4):1721–41.
8. Darveau M, Denault AY, Blais et al. Bench-to-bedside review: iron metabolism in critically ill patients. Crit Care Lond Engl. 2004 Oct;8(5):356–62.
9. Elsayed ME, Sharif MU, Stack AG. Transferrin Saturation: A Body Iron Biomarker. Adv Clin Chem. 2016;75:71–97.
10. Lachmann G, Knaak C, Vorderwülbecke G, et al. Hyperferritinemia in Critically Ill Patients. Crit Care Med. 2020 Apr;48(4):459–65.
11. Marx JJ. Iron and infection: competition between host and microbes for a precious element. *Best practice & research. Clinical haematology.* 2002;**15**:411–426. doi: 10.1053/beha.2002.0001.

12. Bullen J, Griffiths E, Rogers H, Ward G. Sepsis: the critical role of iron. *Microbes and infection.* 2000;**2**:409–415. doi: 10.1016/S1286-4579(00)00326-9.
13. Ganz T. Systemic iron homeostasis. *Physiol Rev.* 2013;**93**:1721–1741.
14. Wallace DF. The Regulation of Iron Absorption and Homeostasis. The Clinical biochemist. Reviews. 2016;37:51–62.
15. Wier L, Pfuntner A, Steiner C. Hospital utilization among oldest adults, 2008: statistical brief #103. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.
16. Lan P, Pan KH, Wang SJ, Shi QC, Yu YX, Fu Y, Chen Y, Jiang Y, Hua XT, Zhou JC, Yu YS. High Serum Iron level is Associated with Increased Mortality in Patients with Sepsis. Sci Rep. 2018 Jul 23;8(1):11072.
17. Brandtner A, Tymoszuk P, Nairz M, Lehner GF, Fritsche G, Vales A, Falkner A, Schennach H, Theurl I, Joannidis M, Weiss G, Pfeifhofer-Obermair C. Linkage of alterations in systemic iron homeostasis to patients' outcome in sepsis: a prospective study. J Intensive Care. 2020 Oct 1;8:76.
18. Ginde AA, Moss M, Shapiro NI, Schwartz RS. Impact of older age and nursing home residence on clinical outcomes of US emergency department visits for severe sepsis. J Crit Care. 2013;28:606–11.
19. Marik PE, Zaloga GP. The effect of aging on circulating levels of proinflammatory cytokines during septic shock. Norasept II Study Investigators. J Am Geriatrics Soc. 2001;49:5–9.
20. Offner PJ, Moore EE, Biffl WL. Male gender is a risk factor for major infections after surgery. *Arch Surg.* 1999;134:935–8, discussion 938-40.
21. McGowan JE, Jr., Barnes MW, Finland M. Bacteremia at Boston City Hospital: Occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. *J Infect Dis.* 1975;132:316–35.
22. Evans L., Rhodes A., Alhazzani W., Antonelli M., Coopersmith C.M., French C., Machado F.R., Mcintyre L., Ostermann M., Prescott H.C., et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021;47:1181–1247.
23. Minasyan H. Sepsis and septic shock: pathogenesis and treatment perspectives. J Crit Care. 2017;18(40):229–242.
24. Thomas-Rüddel DO, Fröhlich H, Schwarzkopf D, Bloos F, Riessen R. Sepsis and underlying comorbidities in intensive care unit patients : Analysis of the cause of death by different clinicians-a pilot study. Med Klin Intensivmed Notfmed. 2024 Mar;119(2):123-128.
25. Bouza C, López-Cuadrado T. Epidemiology and Trends of Sepsis in Young Adults Aged 20-44 Years: A Nationwide Population-Based Study. J Clin Med. 2019 Dec 27;9(1):77.
26. Xia J, Wang F, Jiang X, et al. Serum iron levels are an independent predictor of in-hospital mortality of critically ill patients: a retrospective, single-institution study. Journal of International Medical Research. 2019;47(1):66-75. doi:10.1177/0300060518795528
27. Torti FM, Torti SV. Regulation of ferritin genes and protein. *Blood.* 2002;**99** (10):3505–3516.
28. Cohen LA, Gutierrez L, Weiss A, Leichtmann-Bardoogo Y, Zhang DL, Crooks DR, Sougrat R, Morgenstern A, Galy B, Hentze MW, Lazaro FJ, Rouault TA, Meyron-Holtz EG. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood. 2010 Sep 2;116(9):1574-84.
29. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. Front Immunol. 2019;10:55.
30. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. Crit Care. 2019 Nov 27;23(1):374.
31. Sadaka F, EthmaneAbouElMaali C, Cytron MA, Fowler K, Javaux VM, O'Brien J. Predicting Mortality of Patients With Sepsis: A Comparison of APACHE II and APACHE III Scoring Systems. J Clin Med Res. 2017 Nov;9(11):907-910.