Suspecting Hyperferritinemic Sepsis in Iron-Deficient Population: Do We Need a Lower Plasma Ferritin Threshold?

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Objectives: Hyperferritinemia is being suggested to identify patients with sepsis-induced macrophage activation syndrome for early intervention. However, data among iron-deficient children are scarce. This study was planned to explore the biological behavior of plasma ferritin in children from communities with a high frequency of iron deficiency with septic shock and its association with the outcome.

Design: Prospective observational study.

Setting: Tertiary care teaching hospital in a low-middle income economy of South Asia.

Patients or Subjects: Patients (6 mo to 12 yr) ($n = 42$) with septic shock and their healthy siblings as controls ($n = 36$). Patients/controls with blood transfusion/iron supplement during last 6 months or with any chronic disease were excluded.

Interventions: None.

Measurements and Main Results: Ferritin was measured in patients at enrollment and then at 1 month of hospital discharge while they were not on iron supplementation and in controls as indicative of baseline level. Patients' median age was 30 months (13.5–87 mo), 31% were malnourished, majority (86%) had anemia, and two thirds had microcytic hypochromic red cells. Ferritin at admission was 763 ng/mL (480–1,820 ng/mL) in nonsurvivors, whereas 415 ng/mL (262–852 ng/mL) in survivors ($p = 0.11$). Pediatric Logistic Organ Dysfunction score and *C*-reactive protein correlated positively with plasma ferritin ($p = 0.03$ and $p = 0.01$, respectively) at enrollment. Elevated ferritin of greater than 500 ng/mL (relative risk, 2.48; 95% CI, 0.95–6.43) and greater than 1,000 ng/mL (relative risk, 1.94; 95% CI, 0.94–4.02) were associated with higher mortality but not independently. Among survivors, the 1-month follow-up ferritin fell significantly to 97 ng/mL (16–118 ng/mL) ($p = 0.001$). However, it was still significantly higher than that in sibling controls (19 ng/mL [10–54 ng/mL]) ($p = 0.003$).

Conclusions: Ferritin rises significantly in septic shock patients despite iron deficiency and seems to correlate with the severity of inflammation and organ dysfunction. Even a lower threshold (of 500 or 1,000 ng/mL) could predict higher mortality. It may suggest the need for redefining the plasma ferritin threshold for suspecting hyperferritinemic sepsis and sepsis-induced macrophage activation syndrome in these patients. Larger studies with frequent ferritin measurements are desirable to validate these initial observations. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: iron deficiency anemia; hyperferritinemic sepsis; macrophage activation syndrome; pediatric sepsis; plasma ferritin; septic shock

Sepsis and septic shock are a continuum of the same syndrome caused by infection-induced immune dysregulation and systemic inflammation leading to multiple organ dysfunction syndrome (MODS) (1). Many sepsis patients with MODS fulfilled the criteria of macrophage activation syndrome (MAS) (2) and secondary hemophagocytic lymphohistiocytosis (HLH) (3). Although much of the discussion revolved around the terms of MAS, secondary HLH, and hyperferritnemic sepsis-related MODS (4), currently sepsis, MODS and MAS are being considered as a continuum of increasing severity of immune dysregulation triggered by infections (5). Sepsis-induced MAS (sMAS) is associated with very high mortality among adults (6) as well as among children (7). Halstead et al (8) suggested a paradigm shift from these terminologies to create more inclusive criteria to identify the sickest among sepsis patients at the earliest. It may help to institute prompt immunomodulatory interventions to improve the outcome of an otherwise highly fatal disease. They suggest to use the term "hyperferritinemic sepsis" defined

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by clinical findings and serum ferritin level alone (8), as confirmatory laboratory variables (e.g., soluble interleukin-2Rα, Natural Killer cell activity, and hemophagocytosis in bone marrow) for diagnosis of MAS are difficult to obtain even in developed economies (8, 9).

Carcillo et al (10) reported plasma ferritin (obtained on day 2 of onset) of greater than or equal to 1,980 ng/mL to be associated with very high mortality in children with severe sepsis (6/13 [46%] vs 2/87 [2.3%]). In another study, a peak ferritin of greater than 3,000 ng/mL correlated with increased disease severity (hazard ratio for intensive care admission, 2.49; $p < 0.001$) and higher mortality (hazard ratio for death, 4.32; $p < 0.001$) among largely nonsepsis patients (11). Much higher ferritin levels were reported in patients with sMAS or HLH secondary to infections (7–9, 12). Plasma ferritin level of greater than 10,000 ng/mL was found to be 90% sensitive and 96% specific for the diagnosis of MAS in pediatric patients (9) and thus associated higher mortality. However, in a Brazilian study, much lower ferritin threshold (> 500 ng/mL) was able to predict higher mortality among children with severe sepsis and septic shock (13). Reasoning out these varying thresholds across different studies is needed (10).

Most of the above mentioned data are from North America which has low prevalence (i.e., 3.4%) of iron-deficiency anemia (14), whereas the study reporting association of high mortality with a significantly lower ferritin threshold (of 500 ng/mL) (13) has come from a region with much higher prevalence (i.e., 45%) of iron-deficiency anemia among children (15). The effect of the opposing interplay of iron deficiency and infection on the ferritin level has been appreciated, leading to recommendation of a higher ferritin threshold (30–100 ng/mL) to identify iron-depleted stores among infected patients compared with noninfected ones (i.e., < 12–15 ng/mL) (16). In this background, it is reasonable to consider iron deficiency as one of the key factors which may affect plasma ferritin levels during sepsis/septic shock and sMAS.

The principal aim of this exploratory work was to study the plasma ferritin levels in septic shock children from India having high population prevalence (≃70%) of iron-deficiency anemia (17). Correlation of plasma ferritin with *C*-reactive protein (CRP), organ dysfunction (Pediatric Logistic Organ Dysfunction [PeLOD] score), stay in acute care areas (i.e., emergency department and ICU), and total hospital stay was also studied. An attempt was made to find out a threshold ferritin level at admission to predict mortality in the prevalent situation.

MATERIAL AND METHODS

Clinical Setting and Patients

Our hospital is a federally funded not-for-profit multispecialty tertiary care teaching hospital with 1,740 beds. The catchment area of the hospital includes the surrounding areas of Punjab, Haryana, Himachal Pradesh, and the western part of Uttar Pradesh. A significant proportion of our patients are from families of migrant manual workers from economically poor provinces of Bihar and Uttar Pradesh. Our 24-bedded pediatric emergency department (PER) has about 24,000 visits per year and admits about 12,000 patients per year. The 15-bed PICU admits ≃900 patients and ventilates ≃400 patients per year with bed-occupancy being 100%. We have a 3-year fellowship program in Pediatric Critical Care. PER and PICU are manned by postgraduate pediatric trainees and Pediatric Critical Care fellows under the supervision of Pediatric Critical Care consultants.

This prospective study was performed in PER and PICU over a period of 11 months (May 2016 to March 2017). The inclusion criteria included patients with greater than or equal to 6 months old and less than or equal to 12 years old, who were clinically suspected to have infection and had fluid refractory shock defined as persistence of hypotension (systolic blood pressure < fifth centile for the age) or need for vasoactive drug to maintain blood pressure after greater than 40 mL/kg of isotonic IV fluid therapy in the first hour (18). Patients of less than 6 months were not included as their ferritin status is likely to get affected by the maternal iron status and the physiologic transition from fetal hemoglobin to adult hemoglobin, and patients greater than 12 years do not get admitted to pediatric services at our hospital. As it was an exploratory study, a convenience sample of 40 consecutive patients was planned to be enrolled within 12 hours of PER/PICU documentation of septic shock as far as possible. This was nonfunded dissertation work, to be completed in a limited period, of the postgraduate pediatric training program. It was difficult to screen and enroll all the eligible patients consecutively despite the best efforts of the trainee as he got rotated through various clinical units of the Department of Pediatrics. Thus, a flow diagram showing eligible patients who got enrolled and not enrolled is not provided. Healthy siblings of the patients (age: ≥ 6 mo to ≤ 12 yr; coming from the same family background and sharing the same kitchen) were taken as controls. Patients with parents/guardians not willing to give written consent for enrollment in the study, patient/control sibling having received iron supplementation or blood transfusion during the last 6 months, or having any chronic ailments were excluded from the study. Written informed consent was obtained from parents or legal guardians. The study protocol was approved by the Departmental Review Board, the Institute Ethics Committee, and the Institute Thesis Committee.

Data Collection and Clinical Care of Patients

Enrolled patients had their demographic, clinical (including PeLOD score), and laboratory (complete blood count, red cell indices, and peripheral blood smear examination) data recorded at enrollment. Blood samples were drawn as part of routine clinical care within 12 hours of septic shock identification, and serum CRP (latex-enhanced immunonephelometry; Siemens BN-ProSpec Nephelometer; Siemens, Munich, Germany) and plasma ferritin (chemilumniscence principle; ADVIA Centaur Ferritin System; Siemens Healthcare Diagnostics, Los Angeles, CA) were measured. Patients were initially resuscitated as per the recommended guidelines (19) in PER followed by transfer to PICU as and when the beds became available. Patients were managed as per unit protocol

for hemodynamic support, mechanical ventilation (Hamilton G-5, Hamilton Medical AG, Bonaduz, Switzerland; Maquet Servo-*i*, Maquet Getinge Group, Rastatt, Germany), sedation, nutritional and nursing support. After stabilization in PICU, patients were shifted to pediatric wards from where they got discharged. Microbiological results were collected from medical records. Acute care area free days (ACAFD) at day 14 and ACAFD at day 28, mortality, acute care area stay (PER and PICU), and hospital stay among survivors were recorded as outcome variables. Patients who died in PER or PICU were considered to have "zero" ACAFD at day 14 ($ACAFD_{14}$) and ACAFD at day 28 ($ACAFD_{28}$) as these patients were never free of acute care areas. Instead of PICU-free days, ACAFDs were calculated as many of our patients spend a significant number of days in PER before they could get a place in PICU due to lack of sufficient PICU beds (20). Patients were followed until death or 1 month after discharge from hospital whichever was earlier. Repeat plasma ferritin was obtained after clinically apparent recovery from sepsis (i.e., at 1 mo after discharge from hospital) assuming that plasma ferritin would reach to its baseline value by 1 month. It was ensured that the patients did not receive any iron supplementation during this period. Nutritional status, complete blood count, red cell indices, peripheral blood smear, and serum ferritin were obtained from the controls.

Statistical Analysis

Data were analyzed using SPSS Version 22 (IBM SPSS Statistics, Armonk, NY). Categorical data were presented as number (%), whereas continuous variables were presented as median (interquartile range [IQR]). Continuous and categorical variables were analyzed using Mann-Whitney *U* test (for unpaired data)/Wilcoxon signed-rank test (for paired data) and chi-square test, respectively. Spearman correlation was used to find correlation between serum ferritin at admission and other severity variables of septic shock.

RESULTS

A total of 42 patients with septic shock were enrolled during the study period. We could enroll only 36 children as controls as six patients did not have siblings within the included age group. The septic shock patients were symptomatic for a median duration of 6 days (IQR, 4.0–8.5 d) prior to admission to our hospital. Sixteen patients (38%) had adverse outcome, 14 died in hospital, while two patients were taken against medical advice after having been counseled about irreversibility of the disease process and inevitable death based on the progressive MODS. Demographic, nutritional, and clinical details are shown in **Tables 1** and **2**. The patients were significantly more malnourished compared with their sibling controls. Similarly, the hematologic variables obtained at enrollment were suggestive of higher incidence of and more severe microcytic hypochromic anemia among septic shock patients compared with their sibling controls (**Table 3**).

Median plasma ferritin in sibling controls was 19 (IQR, 10–54) (normal, 50–300 ng/mL). Twenty-six children (72%) had plasma ferritin of less than or equal to 50 ng/mL, whereas 15 (42%) had less than or equal to 15 ng/mL. It suggested significantly depleted iron stores in the siblings. In septic shock patients, the median plasma ferritin at admission was 581 ng/mL (IQR, 287–1,283 ng/mL). Plasma ferritin among nonsurvivors ($n = 16$) was 763 ng/mL (IQR, 480–1,820 ng/mL), whereas among survivors ($n = 26$) it was 415 ng/mL (IQR, 262–852 ng/mL) suggesting a statistically nonsignificant ($p = 0.11$) trend toward higher ferritin levels in nonsurvivors. Patients with ferritin greater than 500 ng/mL (relative risk, 2.48; 95% CI, 0.95–6.43; $p = 0.06$) and greater than 1,000 ng/mL (relative risk, 1.94; 95% CI, 0.94–4.02; $p = 0.07$) had almost a two-fold increase in mortality, although statistically insignificant, compared with those with lower levels.

Median (IQR) CRP was 116.7 mg/L (66.5–239.6 mg/mL), with no difference between survivors and nonsurvivors (121.4 mg/L [60.7–243.3 mg/mL] vs 115.3 mg/L [84.8–227.6 mg/mL]; $p = 0.98$]. Median (IQR) of PeLOD score was 14 (11–22), with nonsurvivors having significantly higher score compared with survivors (22 [12.5–28.3] vs 11 [10–22]; $p = 0.003$). Admission plasma ferritin was positively correlated with CRP (rho = 0.41; $R^2 = 0.073$; $p = 0.01$) and PeLOD score (rho = 0.33; $R^2 = 0.015$; $p = 0.03$) and negatively but nonsignificantly correlated with $ACAFD_{14}$ (rho = –0.25; $p = 0.11$) and $ACAFD_{28}$ (rho = –0.28; $p = 0.07$). Multivariate analysis revealed only PeLOD score, and not the admission ferritin level, to be independently associated with mortality. There was no correlation between total stay in acute care areas or hospital and admission plasma ferritin among survivors. Ferritin level had fallen significantly to median (IQR) of 97 ng/mL (16–118 ng/mL) among survivors after 1 month of discharge from the hospital ($p = 0.001$), up to less than 50 ng/mL in 12 patients and up to less than 15 ng/mL in seven patients. However, 1-month follow-up values were still significantly higher compared with sibling controls ($p = 0.003$).

Six patients had plasma ferritin greater than 2,000 ng/mL (mean, 4,550 ng/mL; range, 2,070–8,224 ng/mL) with diagnosis being scrub typhus ($n = 3$), toxic shock syndrome ($n = 1$), dengue shock syndrome ($n = 1$), and disseminated pyogenic infection ($n = 1$). Their mean CRP and PeLOD scores at admission were 228 mg/L (range, 126–296 mg/L) and 16 mg/L (range, 1–31 mg/L), respectively. Three of them survived; one with scrub typhus (plasma ferritin, 5,325 ng/mL), MODS, and prolonged fever was identified to have hemophagocytosis on bone marrow examination. She was successfully treated with high-dose methylprednisolone. Her ferritin at 1-month follow-up was 10.6 ng/mL, whereas her sibling had ferritin of 18 ng/mL. Surprisingly, another child with scrub typhus, who had the highest ferritin level in the study (i.e., 8,224 ng/mL), had PeLOD score of 1 at admission. However, she went on to develop MODS later during the hospital course and recovered from it without immunomodulatory therapy. Her ferritin at 1-month follow-up was 664 ng/mL, whereas her sibling had ferritin of 56 ng/mL. Two of the three patients who died did so within 48 hours of the admission.

TABLE 1. Demographic and Clinical Characteristics of Patients and Controls

Characteristics	Septic Shock Patients ($n = 42$)	Sibling Controls ($n = 36$)	p
Age, mo, median (IQR)	30.0 (13.5–87.0)	48.0 (36.0–72.0)	0.26
Age, *n* (%), mo			
< 12	5 (12)	01 (3)	NS
12–59	20 (48)	20 (56)	
≥ 60	17 (40)	15 (42)	
Gender ratio (male:female), *n*	22:20	15:21	NS
WAZ, median (IQR)	−1.37 (−2.50 to −0.57)	−0.85 (−1.29 to −0.37)	< 0.01
Number of children with normal nutrition (WAZ > −2 *z*), *n* (%)	29 (69)	33 (92)	0.03
Number of underweight children (WAZ < −2 *z* to −3 *z*), *n* (%)	9 (21)	3 (8)	
Number of severely underweight children (WAZ < −3 *z*), *n* (%)	4 (10)	0 (0)	
HAZ, median (IQR)	−0.94 (−1.65 to −0.39)	−0.85 (−1.09 to −0.18)	NS
Number of children with normal nutrition (HAZ > −2 *z*), *n* (%)	37 (88)	35 (97)	NS
Number of stunted children (HAZ < −2 *z* to −3 *z*), *n* (%)	2 (5)	1 (3)	
Number of severely stunted children (HAZ < −3 *z*), *n* (%)	3 (7)	0 (0)	
Weight for Height *z* score, median (IQR)	−1.30 (−2.00 to −0.11)	−0.55 (−1.43 to 0.44)	0.03
Prehospitalization duration of illness (d), median (IQR)	6.0 (4.0–8.5)	NA	
Pediatric Logistic Organ Dysfunction score, median (IQR)	14 (11–22)	NA	
ACAFD in 14 d, median (IQR)	0.5 (0–7.8)	NA	
ACAFD in 28 d, median (IQR)	14.5 (0–21.8)	NA	
Total hospital stay among septic shock survivors, median (IQR)	14.5 (9–23.3)	NA	

ACAFD = acute care area free days, HAZ = Height for Age *z* score, IQR = interquartile range, NA = not applicable, NS = not significant, WAZ = Weight for Age *z* score.

DISCUSSION

Sepsis continues to remain a public health problem among critically ill children (21) and is the leading cause of death among children, especially under fives of low and middle income economies (22). Global data suggest significant hospital mortality (of 25%) (21) and even higher (> 40%) in tertiary care teaching hospitals of our country (23–25). Septic shock mortality at our institution is reportedly 53% (period, 2013–2014) (26) and 27% (period, 2015–2016) (27). The currently recommended standard of care include appropriate resuscitation with fluid and vasoactive agents, antimicrobials, source control, and support of organ functions (19), paying little attention to the systemic inflammation (10). Infection-induced immune dysregulation leading to sepsis, hyperferritinemia, sMAS, and ultimately MODS is associated with high mortality. It prompts for immunomodulatory therapy early in the management of a select subset of hyperferritinemic sepsis patients (8, 12). However, most of the existing concepts and ferritin thresholds are based on data obtained from populations with very low prevalence of iron deficiency. The current exploratory study provides some insight about how plasma ferritin and other hematologic variables react to sepsis in iron-deficient children. Healthy siblings of the patients (coming from the same family background and sharing the same kitchen) were chosen to be the controls, and three fourth of them had plasma ferritin less than 50 ng/mL (normal reference range, 50–300 ng/mL), which was suggestive of iron deficiency. Ferritin obtained after 1 month of discharge from the hospital among survivors (while not on iron supplementation) continued to remain significantly higher than the sibling controls. It might be indicative of persistence of hyperferritinemia long after subsidence of inflammation as reported among acute lobar pneumonia and pulmonary tuberculosis patients (28). In acute lobar pneumonia, ferritin continued to remain elevated (mean, ≃600 ng/mL) at 15 days of follow-up. Among pulmonary tuberculosis patients, ferritin had fallen (from mean of ≃400 ng/mL) but remained greater than 100 ng/mL at 12–13 weeks of antitubercular treatment. More data are needed to ascertain the natural history of plasma ferritin after a sepsis episode.

During infection, iron homeostasis gets altered by inflammatory cytokines. Despite having iron deficiency, plasma ferritin concentration increases, as ferritin synthesis is more sensitive to inflammatory cytokines than to iron deficiency (16). It was nicely demonstrated in the study population. Median ferritin in study patients was much higher compared

TABLE 2. Clinical Diagnosis and Microbiological Profile of Septic Shock Patients ($n = 42$)

No.	Clinical Diagnosis	*n* (%)
1.	Acute pyogenic infections (disseminated Staphylococcal disease, empyema thoracis, necrotitizing fasciitis)	10 (24)
2.	Culture-negative severe sepsis (without localization)	7 (17)
3.	Scrub typhus (one was diagnosed to have macrophage activation syndrome)	6 (14)
4.	Pneumonia	4 (9.5)
5.	Toxic shock syndrome	4 (9.5)
6.	Acute gastroenteritis	4 (9.5)
7.	Dengue shock syndrome	4 (9.5)
8.	Others	3 (7)
	Total	42 (100)
Positive cultures at admission, *n*		
1.	*Staphylococcus aureus* (blood: 2; pus: 1; blood and pus both: 1)	4
2.	*Staphylococcus* and *β-hemolytic Streptococcus* (throat swab)	1
Culture-positive hospital-acquired infections, *n*		
1.	*Escherichia coli* (blood, day 7)	1
2.	*Ochrobactrum intermedium* (blood, on day 6)	1
3.	*Enterobacter kobei* (blood, on day 8)	1
4.	*Pseudomonas aeruginosa* (blood, on day 5)	1
5.	*E. hemocheii* and *Acinetobacter nosocomialis* (tracheal aspirate, on day 9)	1

Scrub typhus means a rickettsial infection commonly seen in India and caused by *Orientia tsutsugamushi*.

with what reported by Garcia et al (13) (581 ng/mL [287–1,283 ng/mL] vs 303 ng/mL [21–2,210 ng/mL]) despite much higher prevalence of iron-deficiency anemia in the study setting compared with that in Brazil. It is probably due to higher sickness level in the study population. It is further supported by the significant difference in the number of patients having plasma ferritin less than 200 ng/mL in the two studies (36% vs 7%) (**Table 4**).

Elevated plasma ferritin level was helpful in identifying sepsis patients with uncontrolled inflammation/MODS and who had high mortality (8, 10). Sepsis patients with MODS and one/more of inflammation pathobiological phenotypes were reported to have very high ferritin levels (i.e., 3,655 ± 8,654 ng/mL), maximum being greater than 48,000 ng/mL (7). A ferritin level of greater than 1,980 ng/mL, obtained at diagnosis of severe sepsis, was reported to be associated with a 20-fold rise in mortality among patients with presumably normal iron stores (10). These patients are likely to have the so-called "hyperferritinemic sepsis." In contrast, a much lower threshold (500 or 1,000 ng/mL) seems to suggest higher mortality in our iron-deficient patients. Plasma ferritin of greater than 500 ng/mL was associated with 2.5-fold increase in mortality, very similar to what is reported by the Brazilian study (13). Lack of statistical significance was probably due to the small sample size. Ferritin levels even at these lower values were in agreement with the indicators of disease severity, for example, CRP and Organ Dysfunction Score. As multivariate analysis did not reveal admission ferritin to be independently associated with the mortality, it would be difficult to comment whether elevated admission ferritin levels represent a different pathobiology indicative of sMAS in the studied patients. Data on more patients with serial ferritin measurements are needed to ascertain the same. None of our patients with admission ferritin of less than 200 ng/mL died in contrast to what was observed by Garcia et al (13) (Table 4). This observation is at variance with the notion of the beneficial role of a modest elevation in plasma ferritin in sepsis (29).

A majority of the septic shock patients had microcytic hypochromic anemia. Strikingly, these patients were significantly worse compared with their sibling controls in terms of hemoglobin, peripheral smear, and red cell indices (Table 3). Critically ill patients, even from populations with low prevalence of iron-deficiency anemia, reported to become anemic by the end of the first week of their illness (30). This is because of the shortened life span of the red cells due to hemolysis, diminished red cell production due to nutritional deficiencies and "anemia of inflammation." Study patients were sick for a median duration of 6 days (IQR, 4.0–8.5 d) prior to hospitalization, and this prolonged illness might have been sufficient to cause and/or to worsen anemia in nutritionally predisposed children. Another way of looking at this association may be that children with preexisting severe iron deficiency anemia are more likely to develop sepsis once infected. Either way, it needs further exploration and creates doubt about the utility of anemia as one of the classification criteria for sMAS among iron-deficient patients.

Serum ferritin obtained from siblings and from patients 1-month post hospital discharge (while not on iron supplementation) provided an idea about the baseline serum ferritin level among the septic shock patients. We feel that it is essential to appreciate the impact of the two opposing forces, iron deficiency state vis-a-vis sepsis, on plasma ferritin. We, however, are aware of the several limitations of the study. It is out of a dissertation work and thus is of a small sample size. Potential selection bias cannot be ruled out as all consecutive patients could not be screened and enrolled despite the best possible efforts. There was a technical limitation of inability to get ferritin report on the same day for clinical decision-making. Due to the lack of serial ferritin levels, the association of rising ferritin with sequential organ dysfunction could not be appreciated. Serial monitoring of ferritin among patients with initial ferritin of greater than 500 ng/mL may help to identify a subgroup of septic shock patients likely to have the

TABLE 3. Comparative Analysis of Hematologic Variables Between Septic Shock Patients and Sibling Controls

Hematologic Variables	Septic Shock Patients (*n* = 42)	Sibling Controls (*n* = 36)	*p*
Blood hemoglobin (g/dL), median (IQR)	8.9 (7.4–10.2)	11.6 (10.6–12.2)	< 0.01
Anemia (hemoglobin < 11 g/dL), *n* (%)	36 (86)	11 (31)	< 0.0001
Microcytic hypochromic RBCs on peripheral blood smear, *n* (%)	31 (74)	7 (19)	< 0.0001
Mean corpuscular volume (fl), median (IQR)	79 (71–84)	81 (76–84)	0.08
Microcytosis (< 80 fl), *n* (%)	26 (62)	13 (36)	0.04
Mean corpuscular hemoglobin (pg), median (IQR)	25 (22–27)	26 (23–27)	0.17
Hypochromia (< 27 pg), *n* (%)	34 (81)	28 (78)	0.78
Mean corpuscular hemoglobin concentration (%), median (IQR)	31 (29–33)	30 (27–32)	0.01
Hypochromia (< 30%), *n* (%)	13 (31)	19 (53)	0.07
RBC distribution width (%), median (IQR)	17 (15–21)	14 (13–17)	< 0.01
Anisocytosis (> 14%), *n* (%)	38 (90)	16 (44)	< 0.0001

IQR = interquartile range.

TABLE 4. Comparison of Adverse Outcome at Different Cutoffs of Plasma Ferritin in Studies From Two Countries With High Prevalence of Iron Deficiency Anemia

Study/Patient Characteristics	Garcia et al (13) (*n* = 36)		Present Study (*n* = 42)	
Study period	2004–2005		2016–2017	
Country	Brazil		India	
Prevalence of iron deficiency anemia	45 (15)[a]		70 (15)[a]	
Admission Ferritin (ng/mL)	**Number of Patients (%)**	**Proportion Died (%)**	**Number of Patients (%)**	**Proportion Died/Left Against Medical Advice (%)**
< 200	13/36 (36)	23 (03/13)	03/42 (7)	00 (00/03)
200–500	11/36 (31)	9 (01/11)	16/42 (38)	25 (04/16)
≤ 500	24/36 (67)	17 (04/24)	19/42 (45)	21 (04/19)
> 500	12/36 (33)	58 (07/12)	23/42 (55)	52 (12/23)

[a]References (15) and (17) are mentioned in 'Prevalence of iron deficiency anemia' row.

so-called "hyperferritinemic sepsis" and thus higher mortality. Further studies with confirmatory tests for sMAS are suggested among patients having a progressive rise in plasma ferritin and sequential multiple organ failure to help identify sMAS and to find out the predictive plasma ferritin threshold in iron-deficient patients to institute immunomodulatory therapy early.

CONCLUSIONS

Despite the limitation of having a small sample size with a potential selection bias, the study suggests different iron metabolism in iron-deficient sepsis patients. It suggests the need for a different, probably a lower, ferritin threshold to identify "hyperferritinemic sepsis" and to suspect sMAS in patients with a high probability of iron deficiency. With the available data, the "cause or effect" relationship of iron-deficiency anemia with sepsis is difficult to ascertain. Larger studies with serial assessments of ferritin and organ dysfunctions among iron-deficient septic shock patients and confirmatory tests for sMAS among those with initial plasma ferritin of 500 ng/mL or 1,000 ng/mL are desirable to validate these findings.

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