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Correlation of Iron Profile with the Occurrence and Severity of Pneumonia in Children Under Five Years of Age - A Hospital-Based Case - Control Study

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Abstract

Background: Pneumonia remains a leading cause of death in children under five years of age, and iron deficiency anaemia is among the commonest nutritional disorders in the same population. Iron is essential to cell-mediated immunity but is also a growth requirement for pathogenic bacteria, and the direction of the relationship between iron status and pneumonia is therefore not self-evident. This study examined the correlation of the iron profile with the occurrence and severity of pneumonia in under-five children.

Methods: One hundred children aged 6 to 59 months admitted with pneumonia diagnosed by World Health Organization criteria with radiological confirmation were compared with 100 age-matched and sex-matched children without respiratory illness. Haemoglobin, red cell indices, serum iron, serum ferritin, total iron-binding capacity and transferrin saturation were measured, and C-reactive protein was estimated in cases to permit interpretation of ferritin as an acute-phase reactant. Pneumonia severity was graded by World Health Organization criteria.

Study Design: Hospital-based case-control study.

Results: Iron deficiency anaemia was present in 58.0 percent of cases and 24.0 percent of controls (odds ratio 4.37, 95 percent CI 2.38 to 8.03, $p < 0.001$). Mean haemoglobin was 9.42 versus 11.18 g/dL, serum iron 38.6 versus 62.4 microgram/dL and transferrin saturation 11.4 versus 19.8 percent ($p < 0.001$ for each). Severity graded by World Health Organization criteria correlated inversely with haemoglobin (rho = −0.412) and with transferrin saturation (rho = −0.368), and iron deficiency independently predicted severe pneumonia (adjusted odds ratio 3.14, $p = 0.002$).

Conclusion: Iron deficiency was significantly commoner in children with pneumonia and was associated with greater severity. The design cannot establish direction of causation, since acute infection itself lowers serum iron. The findings support screening for iron deficiency in children recovering from pneumonia rather than any inference that iron supplementation during acute infection would be beneficial.

Keywords: Anemia, Iron-Deficiency, Pneumonia, Child, Preschool, Ferritins, Transferrin, Respiratory Tract Infections.

Introduction

Pneumonia remains the single largest infectious cause of death among children under five years of age worldwide, and India carries one of the heaviest absolute burdens of any country. Despite substantial progress in immunisation coverage, case management and access to care, the disease continues to account for a substantial share of paediatric hospital admissions and of under-five mortality in the Indian setting. Efforts to reduce this burden have concentrated on immunisation, on early recognition and appropriate antibiotic treatment, and on the modification of established risk factors, among which malnutrition, indoor air pollution, overcrowding, lack of exclusive breastfeeding and incomplete immunisation are the best characterised.

Iron deficiency anaemia is the commonest nutritional deficiency of childhood and affects a very large proportion of Indian children under five. Its consequences for growth and neurodevelopment are well established. Its relationship with infection is more complex and considerably less settled. Iron is indispensable to several arms of the immune response. Myeloperoxidase, an iron-containing enzyme, is required for the oxidative killing of ingested organisms by neutrophils; ribonucleotide reductase, also iron-dependent, is necessary for lymphocyte proliferation; and iron deficiency has been shown to impair cell-mediated immunity, natural killer cell activity and interleukin - 2 production. On this reasoning, the iron-deficient child would be expected to be more susceptible to respiratory infection.

A substantial body of clinical evidence supports precisely this expectation. Mourad and colleagues reported haemoglobin concentration to be a risk factor for lower respiratory tract infection in Lebanese children, and Malla and colleagues reached a comparable conclusion in a Nepali population.[1,2] A case-control study by Ramakrishnan and Harish identified low haemoglobin as a risk factor for lower respiratory tract infection in Indian children, and Vashishth and colleagues reported similar findings in a subsequent Indian series.[3,4] A systematic review by Hassan and colleagues, examining the association between anaemia and acute respiratory infection, gastroenteritis and urinary tract infection in children under five, concluded that anaemia was consistently associated with acute respiratory infection across the studies reviewed.[5] Reported odds ratios in these studies have generally lain between two and five, an association of considerable magnitude.

The counter-argument is equally serious and is frequently neglected in the Indian literature on this subject. Iron is a growth requirement for most bacterial pathogens, and the mammalian host responds to infection by actively sequestering iron away from the circulation, a process termed nutritional immunity and mediated principally through hepcidin-induced ferroportin internalisation. The resulting hypoferraemia

of inflammation is a defence mechanism, not a deficiency state. This has two immediate consequences for any study of the present kind. First, the low serum iron observed in a child with acute pneumonia may be a consequence of the infection rather than a cause of it, and a case-control design measuring iron parameters during the acute illness cannot distinguish between these possibilities. Second, serum ferritin is an acute-phase reactant that rises in inflammation, so that a child with genuine iron deficiency may present with a ferritin within or above the reference range during acute infection, and ferritin cannot be interpreted without a concurrent measure of inflammation.

The Oxford Iron Supplementation Trial in Pemba demonstrated the practical importance of these considerations, reporting increased hospitalisation and death among iron - replete children given routine iron and folic acid supplementation in a malaria-endemic setting, a finding that led to substantial revision of supplementation policy.[6]

The literature therefore contains a genuine tension. Observational studies consistently associate iron deficiency with respiratory infection, while mechanistic and interventional evidence urges caution about the direction of causation and about the safety of correcting iron deficiency during acute infection. Studies examining the full iron profile, comprising serum iron, ferritin, total iron-binding capacity and transferrin saturation with concurrent measurement of an inflammatory marker, are considerably less common than studies reporting haemoglobin alone, and it is precisely the full profile interpreted alongside inflammation that is required to address the question sensibly. The relationship between iron status and pneumonia severity, as distinct from occurrence, has also received relatively little attention. The present hospital-based case-control study was therefore undertaken to examine the correlation of the iron profile with both the occurrence and the severity of pneumonia in children aged 6 to 59 months, with concurrent measurement of C-reactive protein to permit appropriate interpretation of ferritin.

Aims and Objectives

The study aimed to characterise the relationship between iron status and pneumonia in children under five years of age, examining both the occurrence of disease and its clinical severity. The primary objective was to compare the prevalence of iron deficiency anaemia, defined by haemoglobin, serum ferritin and transferrin saturation criteria, between children aged 6 to 59 months admitted with pneumonia and age-matched and sex-matched children without respiratory illness. The secondary objectives were to compare the individual components of the iron profile, comprising haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, serum iron, serum ferritin, total iron-binding capacity and transferrin saturation, between cases and controls, and to determine the strength of association between iron deficiency and the occurrence of pneumonia expressed as an odds ratio with its confidence interval.

A further objective was to examine the correlation between each component of the iron profile and the severity of pneumonia graded according to World Health Organization criteria, and to determine whether iron deficiency remained independently associated with severe pneumonia after adjustment for age, nutritional status, exclusive breastfeeding, immunisation status and exposure to indoor air pollution. The final objective was to compare the duration of hospital stay, the requirement

for oxygen supplementation and the requirement for intensive care between children with and without iron deficiency among the cases.

Materials and Methods

Study design and setting

This hospital-based case-control study was conducted in the Department of Paediatrics, Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Mandya District, Karnataka, over an eighteen-month period from January 2024 to June 2025.

Approval of the Institutional Ethics Committee was obtained before the commencement of enrolment, and written informed consent was obtained from a parent or legal guardian of every participant. The study was conducted in accordance with the principles of the Declaration of Helsinki and with the National Ethical Guidelines for Biomedical and Health Research Involving Children issued by the Indian Council of Medical Research. Blood sampling in the control group was performed at the time of a venepuncture already clinically indicated, and no child underwent venepuncture solely for the purposes of the study.

Cases

Cases were children aged 6 to 59 months admitted to the paediatric ward with a diagnosis of pneumonia established by World Health Organization Integrated Management of Neonatal and Childhood Illness criteria, comprising cough or difficulty in breathing with age-specific fast breathing or chest in drawing, and confirmed by the presence of consolidation, infiltrates or other features consistent with pneumonia on chest radiography interpreted by a radiologist unaware of the study.

Controls

Controls were children aged 6 to 59 months attending the outpatient department or admitted for a non - infective, non-respiratory reason, individually matched to cases by age within six months and by sex, with no history of acute respiratory infection within the preceding four weeks and no clinical evidence of respiratory illness at examination.

Exclusion criteria

Children in either group were excluded if they had received iron supplementation or a blood transfusion within the preceding three months, since either would render the iron profile uninterpretable. Further exclusions comprised known haemoglobinopathy including sickle cell disease and thalassaemia trait or disease, chronic haemolytic anaemia, congenital heart disease, chronic lung disease including bronchopulmonary dysplasia, bronchial asthma, tuberculosis, chronic kidney or liver disease, known immunodeficiency including human immunodeficiency virus infection, malignancy, severe acute malnutrition with complications requiring inpatient therapeutic feeding, foreign body aspiration, a history of recurrent aspiration, and refusal of consent. Children with bronchiolitis without radiological consolidation were excluded from the case group in order to preserve diagnostic homogeneity.

Sample size calculation

The sample size was calculated for the primary outcome, the difference in the prevalence of iron deficiency anaemia between cases and controls. On the basis of previously published data, the prevalence of iron deficiency anaemia was anticipated to be approximately 55 percent among children with pneumonia and 30 percent among controls.

The formula for the comparison of two independent proportions was applied:

- n per group = $(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [p_1 (1 - p_1) + p_2 (1 - p_2)] / (p_1 - p_2)^2$
- Substituting $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$ for 80 percent power, $p_1 = 0.55$ and $p_2 = 0.30$:
- $n = (2.80)^2 \times [0.2475 + 0.2100] / (0.25)^2$
- $n = 7.84 \times 0.4575 / 0.0625$

$n = 3.5868 / 0.0625 = 57.4$

Fifty-eight participants per group would therefore have sufficed for the primary comparison. The group size was increased to 100 per group, giving a total of 200 participants, in order to provide adequate power for the secondary analysis of pneumonia severity, which required sufficient numbers within severity strata, and to permit multivariable adjustment with an acceptable number of events per variable.

Data collection and laboratory methods

A structured proforma recorded demographic details, birth weight, gestation at birth, exclusive breastfeeding for the first six months, current dietary history with particular attention to the timing of complementary feeding and to the consumption of iron-rich foods and of cow milk, immunisation status verified against the immunisation card, socioeconomic status by the modified Kuppuswamy scale, household crowding, and exposure to indoor air pollution defined as the use of biomass fuel for cooking within the dwelling. Anthropometry comprising weight, length or height and mid-upper arm circumference was recorded and plotted against World Health Organization growth standards, and nutritional status was classified by weight-for-age, height-for-age and weight-for-height Z scores.

Venous blood was drawn at admission in cases, before the administration of any parenteral therapy, and at the time of a clinically indicated venepuncture in controls. Complete blood count with red cell indices was performed on an automated haematology analyser. Serum iron and total iron-binding capacity were estimated by the ferrozine colorimetric method, and serum ferritin by chemiluminescent immunoassay. Transferrin saturation was calculated as serum iron divided by total iron-binding capacity, expressed as a percentage. C-reactive protein was measured in all cases by immunoturbidimetry, in order to permit interpretation of ferritin in the presence of acute inflammation.

Definitions

Anaemia was defined according to World Health Organization criteria as a haemoglobin below 11.0 g/dL in children aged 6 to 59 months. Iron deficiency was defined by a serum ferritin below 12 ng/mL, or below 30 ng/mL where the C-reactive protein exceeded 5 mg/L in recognition of the acute-phase elevation of ferritin, together with a transferrin saturation below 16 percent. Iron deficiency anaemia was diagnosed where anaemia and iron deficiency coexisted. Pneumonia severity was graded according to World Health Organization criteria, with pneumonia denoting fast breathing or chest in drawing without danger signs and severe pneumonia denoting the presence of any general danger sign, comprising inability to drink or breastfeed, persistent vomiting, convulsions, lethargy or unconsciousness, central cyanosis or severe respiratory distress.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 26.0. Normality was assessed by the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean with standard deviation and compared by the independent samples Student t test, and non-normally distributed

variables as median with interquartile range and compared by the Mann-Whitney U test. Categorical variables were expressed as frequencies with percentages and compared by the Pearson chi-square test, with the Fisher exact test where any expected cell frequency was below five. The strength of association between iron deficiency and pneumonia was expressed as an odds ratio with a 95 percent confidence interval. The correlation between iron parameters and pneumonia severity was examined by the Spearman rank correlation coefficient, severity being an ordinal variable. Variables associated with severe pneumonia at p below 0.10 on univariate analysis were entered into a multivariable binary logistic regression model, and adjusted odds ratios were reported with 95 percent confidence intervals. A two-tailed p value below 0.05 was considered statistically significant.

Results

Baseline characteristics

Two hundred and eighteen children were assessed for eligibility, of whom 18 were excluded, seven for recent iron supplementation, four for known haemoglobinopathy, three for congenital heart disease, two for tuberculosis and two for refusal of consent. Two hundred children were enrolled, comprising 100 cases and 100 individually matched controls. The mean age was 24.6 ± 14.2 months among cases and 25.1 ± 14.6 months among controls (t = 0.25, p = 0.806), and 58 children (58.0 percent) in each group were male, matching having been performed on both variables.

Several risk factors differed significantly between the groups. Exclusive breastfeeding for the first six months had been practised in 52 cases (52.0 percent) and 71 controls (71.0 percent) (χ^2 = 7.66, p = 0.006). Complete immunisation for age was documented in 78 cases (78.0 percent) and 91 controls (91.0 percent) (χ^2 = 6.66, p = 0.010). Exposure to biomass fuel smoke within the dwelling was reported in 46 cases (46.0 percent) and 29 controls (29.0 percent) (χ^2 = 6.13, p = 0.013). Underweight status with a weight-for-age Z score below −2 was present in 38 cases (38.0 percent) and 21 controls (21.0 percent) (χ^2 = 6.94, p = 0.008). Overcrowding and lower socioeconomic class were also commoner among cases. Baseline characteristics are presented in Table 1.

Haematological and iron parameters

All measured iron parameters differed significantly between the groups. The mean haemoglobin was 9.42 ± 1.68 g/dL among cases and 11.18 ± 1.42 g/dL among controls (t = 7.99, p < 0.001). The mean corpuscular volume was 68.4 ± 8.2 fL and 76.8 ± 7.4 fL (t = 7.60, p < 0.001), and the mean corpuscular haemoglobin 21.6 ± 3.4 pg and 25.2 ± 3.1 pg (t = 7.82, p < 0.001). The red cell distribution width was 17.42 ± 2.86 percent and 14.68 ± 2.24 percent (t = 7.54, p < 0.001).

The mean serum iron was 38.6 ± 16.4 microgram/dL among cases and 62.4 ± 19.8 microgram/dL among controls (t = 9.26, p < 0.001), and the mean total iron-binding capacity was 412 ± 68 microgram/dL and 358 ± 62 microgram/dL respectively (t = 5.87, p < 0.001). Transferrin saturation was 11.4 ± 5.6 percent among cases and 19.8 ± 7.2 percent among controls (t = 9.21, p < 0.001). The median serum ferritin was 28.4 ng/mL with an interquartile range of 14.2 to 52.6 among cases and 22.6 ng/mL with an interquartile range of 12.8 to 38.4 among controls, a difference in the opposite direction to that of the other parameters which did not reach statistical significance (U = 4386.0, p = 0.114). This apparent discordance is attributable to the acute-phase elevation of ferritin, and the median C-reactive

protein among cases was 48.6 mg/L with an interquartile range of 22.4 to 86.2. Among the 62 cases with a C-reactive protein above 5 mg/L, the median ferritin was 34.8 ng/mL compared with 16.2 ng/mL among the 38 cases with a C-reactive protein of 5 mg/L or below (U = 682.5, p < 0.001). Haematological and iron data are set out in Table 2.

Prevalence of iron deficiency and strength of association

Anaemia was present in 76 cases (76.0 percent) and 42 controls (42.0 percent) (χ^2 = 23.83, p < 0.001). Iron deficiency, defined by ferritin and transferrin saturation criteria with adjustment for C-reactive protein, was present in 64 cases (64.0 percent) and 31 controls (31.0 percent) (χ^2 = 21.83, p < 0.001). Iron deficiency anaemia, requiring both criteria, was present in 58 cases (58.0 percent) and 24 controls (24.0 percent), yielding an odds ratio of 4.37 with a 95 percent confidence interval of 2.38 to 8.03 (χ^2 = 24.06, p < 0.001).

When stratified by age, the association was strongest in the 6 to 23-month stratum, in which iron deficiency anaemia was present in 34 of 52 cases (65.4 percent) and 14 of 53 controls (26.4 percent), and was weaker though still significant in the 24 to 59-month stratum, in which it was present in 24 of 48 cases (50.0 percent) and 10 of 47 controls (21.3 percent). The Mantel-Haenszel pooled odds ratio adjusted for age stratum was 4.28 with a 95 percent confidence interval of 2.32 to 7.89. Prevalence and association data are detailed in Table 3.

Iron status and pneumonia severity

Among the 100 cases, 62 children (62.0 percent) had pneumonia and 38 children (38.0 percent) had severe pneumonia by World Health Organization criteria. Iron parameters differed significantly between these severity strata. The mean haemoglobin was 10.06 ± 1.42 g/dL in those with pneumonia and 8.38 ± 1.48 g/dL in those with severe pneumonia (t = 5.66, p < 0.001), the mean serum iron 43.8 ± 15.2 and 30.2 ± 14.6 microgram/dL (t = 4.44, p < 0.001), and transferrin saturation 13.2 ± 5.2 and 8.4 ± 4.6 percent (t = 4.72, p < 0.001).

Spearman rank correlation confirmed an inverse relationship between iron status and severity. Severity correlated negatively with haemoglobin (rho = −0.412, p < 0.001), with transferrin saturation (rho = −0.368, p < 0.001), with serum iron (rho = −0.354, p < 0.001) and with mean corpuscular volume (rho = −0.286, p = 0.004), and positively with total iron-binding capacity (rho = 0.268, p = 0.007) and with red cell distribution width (rho = 0.242, p = 0.015). The correlation with serum ferritin was positive and weak (rho = 0.198, p = 0.048), again reflecting its behaviour as an acute-phase reactant rather than any protective association.

Iron deficiency anaemia was present in 30 of 62 children with pneumonia (48.4 percent) and 28 of 38 children with severe pneumonia (73.7 percent) (χ^2 = 6.15, p = 0.013). On multivariable logistic regression, iron deficiency anaemia remained independently associated with severe pneumonia after adjustment (adjusted odds ratio 3.14, 95 percent confidence interval 1.52 to 6.49, p = 0.002), as did underweight status (adjusted odds ratio 2.46, 95 percent confidence interval 1.18 to 5.13, p = 0.016) and age below 24 months (adjusted odds ratio 2.08, 95 percent confidence interval 1.02 to 4.24, p = 0.044). Exclusive breastfeeding was protective (adjusted odds ratio 0.48, 95 percent confidence interval 0.23 to 0.99, p = 0.047). Severity data appear in Tables 4 and 5.

Clinical course among cases

Among the 100 cases, those with iron deficiency anaemia had a longer duration of hospital stay at 6.8 ± 2.6 days compared with 4.9 ± 2.1 days in those without

(t = 3.85, p < 0.001), a greater requirement for supplemental oxygen at 34 of 58 (58.6 percent) compared with 12 of 42 (28.6 percent) (χ^2 = 8.89, p = 0.003), and a longer duration of oxygen therapy among those requiring it at 48.6 ± 22.4 hours compared with 32.4 ± 18.6 hours (t = 2.62, p = 0.012). Admission to the paediatric intensive care unit was required by 11 children with iron deficiency anaemia (19.0 percent) and 3 children without (7.1 percent), a difference that did not reach statistical significance (χ^2 = 2.91, p = 0.088). Two deaths occurred, both in children with iron deficiency anaemia and severe pneumonia. Clinical course data are presented in Table 6.

Tables

Table 1: Baseline demographic, nutritional and environmental characteristics of cases and controls (N = 200)

Variable	Cases (n = 100)	Controls (n = 100)	Test statistic	p value
Age, months (mean ± SD)	24.6 ± 14.2	25.1 ± 14.6	t = 0.25	0.806
Age 6–23 months, n (%)	52 (52.0)	53 (53.0)	χ^2 = 0.02	0.888
Male sex, n (%)	58 (58.0)	58 (58.0)	Matched	—
Birth weight <2500 g, n (%)	27 (27.0)	19 (19.0)	χ^2 = 1.79	0.181
Preterm birth, n (%)	14 (14.0)	9 (9.0)	χ^2 = 1.24	0.266
Exclusive breastfeeding 6 months, n (%)	52 (52.0)	71 (71.0)	χ^2 = 7.66	0.006
Complete immunisation for age, n (%)	78 (78.0)	91 (91.0)	χ^2 = 6.66	0.010
Weight-for-age Z score < −2, n (%)	38 (38.0)	21 (21.0)	χ^2 = 6.94	0.008
Height-for-age Z score < −2, n (%)	31 (31.0)	18 (18.0)	χ^2 = 4.55	0.033
Mid-upper arm circumference <12.5 cm, n (%)	24 (24.0)	11 (11.0)	χ^2 = 5.98	0.014
Biomass fuel exposure indoors, n (%)	46 (46.0)	29 (29.0)	χ^2 = 6.13	0.013
Overcrowding (>2 persons per room), n (%)	41 (41.0)	26 (26.0)	χ^2 = 5.03	0.025
Lower socioeconomic class (Kuppuswamy IV–V), n (%)	58 (58.0)	44 (44.0)	χ^2 = 3.92	0.048
Cow milk before 12 months, n (%)	44 (44.0)	31 (31.0)	χ^2 = 3.60	0.058
Maternal education below secondary, n (%)	49 (49.0)	38 (38.0)	χ^2 = 2.46	0.117

SD, standard deviation. Cases and controls were individually matched by age within six months and by sex.

Table 2: Haematological and iron profile parameters in cases and controls (N = 200)

Parameter	Cases (n = 100)	Controls (n = 100)	Test statistic	p value
Haemoglobin, g/dL (mean ± SD)	9.42 ± 1.68	11.18 ± 1.42	t = 7.99	<0.001
Mean corpuscular volume, fL (mean ± SD)	68.4 ± 8.2	76.8 ± 7.4	t = 7.60	<0.001
Mean corpuscular haemoglobin, pg (mean ± SD)	21.6 ± 3.4	25.2 ± 3.1	t = 7.82	<0.001
MCHC, g/dL (mean ± SD)	30.8 ± 2.2	32.6 ± 2.0	t = 6.05	<0.001
Red cell distribution width, % (mean ± SD)	17.42 ± 2.86	14.68 ± 2.24	t = 7.54	<0.001

Serum iron, µg/dL (mean ± SD)	38.6 ± 16.4	62.4 ± 19.8	t = 9.26	<0.001
Total iron-binding capacity, µg/dL (mean ± SD)	412 ± 68	358 ± 62	t = 5.87	<0.001
Transferrin saturation, % (mean ± SD)	11.4 ± 5.6	19.8 ± 7.2	t = 9.21	<0.001
Serum ferritin, ng/mL, median (IQR)	28.4 (14.2–52.6)	22.6 (12.8–38.4)	U = 4386.0	0.114
C-reactive protein, mg/L, median (IQR)*	48.6 (22.4–86.2)	Not measured	—	—
Ferritin if CRP >5 mg/L, ng/mL, median*	34.8	—	U = 682.5	<0.001
Ferritin if CRP ≤5 mg/L, ng/mL, median*	16.2	—		
Total leucocyte count, /mm³ (mean ± SD)	14,860 ± 5,240	8,420 ± 2,180	t = 11.34	<0.001

SD, standard deviation; IQR, interquartile range; MCHC, mean corpuscular haemoglobin concentration; CRP, C-reactive protein. *Measured in cases only; the ferritin comparison by CRP stratum is within cases (62 with CRP >5 mg/L, 38 with CRP ≤5 mg/L).

Table 3: Prevalence of anaemia and iron deficiency and strength of association with pneumonia (N = 200)

Category	Cases (n = 100)	Controls (n = 100)	Odds ratio (95% CI)	p value
Anaemia (Hb <11 g/dL), n (%)	76 (76.0)	42 (42.0)	4.37 (2.38–8.03)	<0.001
Iron deficiency, n (%)	64 (64.0)	31 (31.0)	3.96 (2.21–7.09)	<0.001
Iron deficiency anaemia, n (%)	58 (58.0)	24 (24.0)	4.37 (2.38–8.03)	<0.001
Severe anaemia (Hb <7 g/dL), n (%)	14 (14.0)	3 (3.0)	5.26 (1.46–18.94)	0.006
Microcytic hypochromic picture, n (%)	61 (61.0)	27 (27.0)	4.23 (2.34–7.64)	<0.001
Iron deficiency anaemia by age stratum				
6–23 months	34/52 (65.4)	14/53 (26.4)	5.26 (2.28–12.15)	<0.001
24–59 months	24/48 (50.0)	10/47 (21.3)	3.70 (1.51–9.07)	0.004
Mantel-Haenszel pooled	—	—	4.28 (2.32–7.89)	<0.001

CI, confidence interval; Hb, haemoglobin. Iron deficiency was defined by serum ferritin below 12 ng/mL, or below 30 ng/mL where C-reactive protein exceeded 5 mg/L, together with transferrin saturation below 16 percent.

Table 4: Iron parameters by World Health Organization pneumonia severity grade among cases (n = 100)

Parameter	Pneumonia (n = 62)	Severe pneumonia (n = 38)	Test statistic	p value
Haemoglobin, g/dL (mean ± SD)	10.06 ± 1.42	8.38 ± 1.48	t = 5.66	<0.001
Mean corpuscular volume, fL (mean ± SD)	70.8 ± 7.6	64.6 ± 8.0	t = 3.90	<0.001
Serum iron, µg/dL (mean ± SD)	43.8 ± 15.2	30.2 ± 14.6	t = 4.44	<0.001
Total iron-binding capacity, µg/dL (mean ± SD)	396 ± 62	438 ± 70	t = 3.13	0.002
Transferrin saturation, % (mean ± SD)	13.2 ± 5.2	8.4 ± 4.6	t = 4.72	<0.001
Red cell distribution width, % (mean ± SD)	16.84 ± 2.62	18.36 ± 2.94	t = 2.68	0.009
Serum ferritin, ng/mL, median (IQR)	24.6 (13.4–46.8)	36.2 (18.6–64.4)	U = 897.0	0.048
C-reactive protein, mg/L, median (IQR)	38.4 (18.6–68.2)	68.4 (36.2–112.6)	U = 786.5	0.004

Iron deficiency anaemia, n (%)	30 (48.4)	28 (73.7)	$\chi^2 = 6.15$	0.013
Severe anaemia (Hb <7 g/dL), n (%)	4 (6.5)	10 (26.3)	$\chi^2 = 7.79$	0.005

SD, standard deviation; IQR, interquartile range; Hb, haemoglobin. Severity graded by World Health Organization criteria; severe pneumonia denotes the presence of any general danger sign.

Table 5: Correlation with severity and multivariable predictors of severe pneumonia among cases (n = 100)

Variable	Spearman rho	p value	Adjusted OR (95% CI)	p value
Haemoglobin	−0.412	<0.001	—	—
Transferrin saturation	−0.368	<0.001	—	—
Serum iron	−0.354	<0.001	—	—
Mean corpuscular volume	−0.286	0.004	—	—
Total iron-binding capacity	0.268	0.007	—	—
Red cell distribution width	0.242	0.015	—	—
Serum ferritin	0.198	0.048	—	—
Multivariable logistic regression				
Iron deficiency anaemia	—	—	3.14 (1.52–6.49)	0.002
Weight-for-age Z score < −2	—	—	2.46 (1.18–5.13)	0.016
Age <24 months	—	—	2.08 (1.02–4.24)	0.044
Exclusive breastfeeding 6 months	—	—	0.48 (0.23–0.99)	0.047
Biomass fuel exposure	—	—	1.74 (0.84–3.61)	0.137
Incomplete immunisation	—	—	1.62 (0.71–3.70)	0.252

OR, odds ratio; CI, confidence interval. Spearman correlations are with World Health Organization severity grade as an ordinal variable. Model summary: overall $\chi^2 = 28.4$, degrees of freedom 6, $p < 0.001$; Hosmer - Lemeshow $\chi^2 = 5.82$, degrees of freedom 8, $p = 0.667$; Nagelkerke $R^2 = 0.342$.

Table 6: Clinical course among cases stratified by iron deficiency anaemia (n = 100)

Outcome	IDA present (n = 58)	IDA absent (n = 42)	Test statistic	p value
Severe pneumonia, n (%)	28 (48.3)	10 (23.8)	$\chi^2 = 6.15$	0.013
Duration of hospital stay, days (mean ± SD)	6.8 ± 2.6	4.9 ± 2.1	t = 3.85	<0.001
Supplemental oxygen required, n (%)	34 (58.6)	12 (28.6)	$\chi^2 = 8.89$	0.003
Duration of oxygen therapy, h (mean ± SD)*	48.6 ± 22.4	32.4 ± 18.6	t = 2.62	0.012
PICU admission, n (%)	11 (19.0)	3 (7.1)	$\chi^2 = 2.91$	0.088
Mechanical ventilation, n (%)	4 (6.9)	1 (2.4)	Fisher exact	0.394
Time to defervescence, days (mean ± SD)	3.6 ± 1.4	2.8 ± 1.2	t = 2.98	0.004
Change of antibiotic required, n (%)	13 (22.4)	5 (11.9)	$\chi^2 = 1.83$	0.176

Death, n (%)	2 (3.4)	0 (0.0)	Fisher exact	0.508

IDA, iron deficiency anaemia; SD, standard deviation; PICU, paediatric intensive care unit. *Computed among the 46 children who required supplemental oxygen (34 with IDA, 12 without).

Discussion

This hospital-based case-control study found iron deficiency anaemia to be substantially commoner among children under five admitted with pneumonia than among matched controls, with an odds ratio of 4.37, and found iron status to correlate inversely with the severity of pneumonia, iron deficiency anaemia remaining independently associated with severe disease after adjustment for nutritional status, age, breastfeeding, immunisation and indoor air pollution.

The magnitude of the association observed here is consistent with the published literature. Mourad and colleagues reported haemoglobin concentration to be a risk factor for lower respiratory tract infection in Lebanese children, and Malla and colleagues reported a comparable finding in Nepal.[1,2] Ramakrishnan and Harish, in an Indian population, and Vashishth and colleagues, in a subsequent Indian series, both identified anaemia as a risk factor for lower respiratory tract infection with odds ratios of similar magnitude to that found here.[3,4] The systematic review of Hassan and colleagues, which examined the relationship between anaemia and acute respiratory infection among children under five, concluded that the association was consistent across the studies reviewed.[5] The present finding of an association that was strongest in the 6 to 23 month stratum is biologically coherent, since this is the period during which iron stores accumulated in utero become exhausted, complementary feeding is often inadequate in iron, and susceptibility to respiratory infection is at its peak.

The central interpretative difficulty of this study, and of every study of this design, is the direction of causation. Two mechanisms could generate the association observed, and the data cannot distinguish between them. The first is that iron deficiency impairs immune function and thereby predisposes to pneumonia; this is supported by the established roles of iron in myeloperoxidase-dependent oxidative killing, in ribonucleotide reductase-dependent lymphocyte proliferation, and in natural killer cell activity. The second is that acute infection lowers serum iron through hepcidin-mediated sequestration, a defensive response termed nutritional immunity, so that the low serum iron and low transferrin saturation observed in cases would be a consequence of the pneumonia rather than a cause of it. The present data in fact contain direct evidence of this second process operating: serum ferritin, alone among the parameters measured, was numerically higher in cases than in controls, and among cases the median ferritin was more than twice as high in those with a raised C-reactive protein as in those without. This is exactly the pattern predicted by acute-phase behaviour, and it should caution against reading the whole of the observed association as evidence that deficiency causes infection.

This caution has direct practical consequences and is why the interventional literature must be considered alongside the observational. The Pemba trial reported increased hospitalisation and death among iron-replete children given routine iron and folic acid supplementation in a malaria-endemic setting, a finding that prompted revision of supplementation policy and that is generally understood in terms of increased iron

availability to pathogens.[6] A Cochrane review of iron supplementation in children living in malaria-endemic areas reached broadly consistent conclusions regarding the need for concurrent malaria control.[7] It would therefore be a serious misreading of the present findings to conclude that iron should be administered to children during an episode of acute pneumonia. The defensible inference is narrower and, in the Indian context, still useful: that children recovering from pneumonia constitute a group with a high prevalence of genuine iron deficiency and merit screening and treatment once the acute illness has resolved and inflammatory markers have normalised.

The association between iron status and severity, as distinct from occurrence, is less well documented in the published literature and merits comment. Several mechanisms plausibly contribute. Anaemia reduces oxygen-carrying capacity, so that a given degree of ventilation-perfusion mismatch produces greater tissue hypoxia in the anaemic child, and the compensatory tachycardia and increased cardiac output impose an additional burden. Impaired cell-mediated immunity may permit more extensive consolidation. The association may also be partly confounded, since severity and anaemia share determinants including undernutrition and lower socioeconomic status, and although the multivariable model adjusted for underweight status and socioeconomic class, residual confounding cannot be excluded. The longer hospital stay and greater oxygen requirement observed among iron-deficient cases are consistent with the severity association and carry direct implications for the anticipated burden on ward and oxygen resources.

The other risk factors identified, comprising the absence of exclusive breastfeeding, incomplete immunisation, exposure to biomass fuel smoke and underweight status, are well established determinants of childhood pneumonia and their identification in this cohort strengthens confidence in the internal validity of the data. That exclusive breastfeeding retained independent protective significance in the multivariable model, with an adjusted odds ratio of 0.48, is worth emphasising in a district and rural setting, since it is a modifiable factor requiring no purchased commodity.

Limitations

The limitations of this study are substantial and must be stated plainly. The case-control design cannot establish the direction of causation, and the acute-phase response demonstrably influenced at least one of the parameters measured, so the observed association between low iron indices and pneumonia is not evidence that iron deficiency causes pneumonia. A prospective cohort measuring iron status before the onset of infection, or a randomised trial of correction of deficiency in the convalescent period, would be required to address this question. Iron parameters were measured during the acute illness, which is the fundamental design weakness; measurement repeated after recovery would have permitted the deficiency and the sequestration components to be separated, and this was not undertaken. Only C-reactive protein was available as an inflammatory marker, whereas soluble transferrin receptor, which is relatively unaffected by inflammation, would have been the appropriate index of tissue iron status. Hepcidin was not measured. Controls were drawn from a hospital population and may not represent the community from which the cases arose. Dietary and breastfeeding histories were obtained by recall and are subject to recall bias, which may be differential between the parents of a sick and a well-child. Bacteriological

confirmation of the aetiology of pneumonia was not obtained in the majority of cases, so no comment can be made on whether the association differs by causative organism. Finally, the study was conducted at a single centre in a rural catchment with a high background prevalence of both anaemia and pneumonia, and the effect estimates may not transfer to populations with a Different Baseline Burden.

Conclusion

Iron deficiency anaemia was present in 58.0 percent of children under five admitted with pneumonia compared with 24.0 percent of matched controls, an odds ratio of 4.37, and iron status correlated inversely with pneumonia severity, with iron deficiency anaemia remaining independently associated with severe pneumonia after adjustment for nutritional status, age, breastfeeding, immunisation and indoor air pollution. Iron-deficient children with pneumonia required oxygen more often and remained in hospital longer.

These findings should be read for what they are. The design establishes association and not causation, and the behaviour of serum ferritin in this cohort provides direct evidence that acute infection itself alters iron indices, so that part of the observed difference is a consequence of the pneumonia rather than a cause of it. The practical implication is therefore not that iron should be given during acute pneumonia, a course against which the interventional literature in infection-endemic settings advises caution, but that children admitted with pneumonia represent a readily identifiable group with a very high prevalence of iron deficiency who should be screened after recovery, when inflammatory markers have settled, and treated accordingly. Attention to exclusive breastfeeding, completion of immunisation and reduction of household biomass smoke exposure remain the interventions with the clearest evidence of benefit for the prevention of pneumonia itself. Prospective cohort studies measuring iron status before infection, with soluble transferrin receptor and hepcidin alongside conventional indices, are needed to establish whether the relationship is causal.

References

1. Mourad S, Rajab M, Alameddine A, Fares M, Ziade F, Merhi BA. Hemoglobin level as a risk factor for lower respiratory tract infections in Lebanese children. N Am J Med Sci. 2010; 2(10):461-6.
2. Malla T, Pathak OK, Malla KK. Is low haemoglobin level a risk factor for acute lower respiratory tract infections? J Nepal Paediatr Soc. 2010; 30 (1):1-7.
3. Ramakrishnan K, Harish PS. Hemoglobin level as a risk factor for lower respiratory tract infections. Indian J Pediatr. 2006; 73(10):881-3.
4. Vashishth D, Sharma GL, Masand R. Anemia as a risk factor for lower respiratory tract infection in children of 6 months to 5 years of age. Indian J Child Health. 2019; 6(3):113-6.
5. Hassan TH, Badr MA, Karam NA, Zkaria M, El Saadany HF, Abdel Rahman DM, et al. Impact of iron deficiency anemia on the function of the immune system in children. Medicine (Baltimore). 2016;95(47):e5395.
6. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006; 367 (9505):133-43.

7. Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev. 2016; 2:CD006589.

8. Bhaskaram P, Madhavan Nair K, Balakrishna N, Ravinder P, Sesikeran B. Serum transferrin receptor in children with respiratory infections. Eur J Clin Nutr. 2003;57(1):75-80.

9. Broor S, Pandey RM, Ghosh M, Maitreyi RS, Lodha R, Singhal T, et al. Risk factors for severe acute lower respiratory tract infection in under-five children. Indian Pediatr. 2001;38(12):1361-9.

10. Ganz T, Nemeth E. Iron homeostasis in host defence and inflammation. Nat Rev Immunol. 2015; 15 (8):500-10.

11. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. Science. 2012; 338(6108):768-72.

12. World Health Organization. Revised WHO classification and treatment of childhood pneumonia at health facilities: evidence summaries. Geneva: World Health Organization; 2014.

13. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011.

14. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. Am J Clin Nutr. 2010; 92 (3):546-55.

15. Ekiz C, Agaoglu L, Karakas Z, Gurel N, Yalcin I. The effect of iron deficiency anemia on the function of the immune system. Hematol J. 2005; 5(7):579-83.

16. Jonker FA, Calis JC, van Hensbroek MB, Phiri K, Geskus RB, Brabin BJ, et al. Iron status predicts malaria risk in Malawian preschool children. PLoS One. 2012; 7 (8):e42670.

17. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006; 64 (5 Pt 2):S34-43.

18. Koch A, Molbak K, Homoe P, Sorensen P, Hjuler T, Olesen ME, et al. Risk factors for acute respiratory tract infections in young Greenlandic children. Am J Epidemiol. 2003;158(4):374-84.