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Original Research Article

Predictors of Delayed Clinical Recovery in Children with Typhoid Fever

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Abstract

Background: Typhoid fever remains an important cause of morbidity among children, and a proportion of patients experience prolonged illness and delayed clinical recovery despite appropriate treatment. Identification of predictors of delayed recovery may facilitate early recognition and appropriate management of high-risk children.

Objective: To identify clinical, laboratory, demographic, microbiological, and treatment-related predictors of delayed clinical recovery in children with typhoid fever.

Materials and Methods: A hospital-based observational study was conducted in the Department of Paediatrics at a tertiary care teaching hospital over a period of 1 year. A total of 100 children aged ≤18 years diagnosed with typhoid fever were included. Demographic, clinical, laboratory, microbiological, and treatment-related data were collected using a structured proforma. Patients were categorised into early and delayed clinical recovery groups. Factors associated with delayed recovery were evaluated using univariate analysis, followed by multivariable logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and a p-value <0.05 was considered statistically significant.

Results: Of the 100 children, 68 (68.0%) achieved early recovery, while 32 (32.0%) had delayed recovery. Delayed recovery was significantly associated with fever >7 days before presentation, high-grade fever, hepatomegaly, splenomegaly, dehydration, elevated AST and ALT, and antibiotic modification. On multivariable logistic regression, fever >7 days before presentation (adjusted OR 3.02; 95% CI: 1.18–7.73; p=0.020), dehydration (adjusted OR 2.91; 95% CI: 1.01–8.38; p=0.048), elevated ALT (adjusted OR 2.76; 95% CI: 1.04–7.34; p=0.042), and antibiotic modification (adjusted OR 2.89; 95% CI: 1.02–8.18; p=0.046) were identified as independent predictors of delayed clinical recovery.

Conclusion: Delayed clinical recovery occurred in nearly one-third of children with typhoid fever. Prolonged fever before presentation, dehydration, elevated ALT, and antibiotic modification were independent predictors of delayed recovery. Early identification of these factors may help in risk stratification, closer monitoring, and timely management of pediatric typhoid fever.

Keywords: Typhoid fever; children; delayed recovery; predictors; dehydration; ALT; antibiotic modification; enteric fever.

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Introduction

Typhoid fever, also known as enteric fever, is a systemic bacterial infection caused predominantly by *Salmonella enterica* serovar Typhi and remains an important public health concern in developing countries. The disease is particularly prevalent in regions with inadequate sanitation, unsafe drinking water, and poor hygienic conditions. South Asia contributes substantially to the global burden of enteric fever, with children representing an important affected population [1,2].

In children, typhoid fever may present with a wide spectrum of clinical manifestations ranging from uncomplicated febrile illness to severe systemic disease. Prolonged fever is the most characteristic feature, while gastrointestinal manifestations such as abdominal pain, vomiting, diarrhea, and constipation may occur. Hepatomegaly and splenomegaly are also frequently described, particularly among hospitalized children [3,4]. Hematological abnormalities including anemia, leukopenia, thrombocytopenia, and abnormalities of liver enzymes may accompany the infection and can provide useful indicators of disease severity [5].

Although most children respond to appropriate antimicrobial therapy, some experience prolonged fever and delayed resolution of clinical symptoms. Delayed recovery can increase the duration of hospitalization, healthcare utilization, and risk of complications. Factors such as delayed presentation, prolonged duration of fever before treatment, dehydration, gastrointestinal manifestations, hepatic involvement, and inadequate response to initial antimicrobial therapy may contribute to a slower clinical recovery [6,7].

The emergence and spread of antimicrobial-resistant *S. Typhi* has further complicated the management of enteric fever. Resistance to commonly used antibiotics, including fluoroquinolones and third-generation cephalosporins, has been increasingly reported, while extensively drug-resistant typhoid strains have created additional therapeutic challenges in South Asia [8,9]. Consequently, early recognition of patients who may have delayed clinical response and appropriate selection of effective antimicrobial therapy are important components of pediatric typhoid management.

Previous studies have primarily focused on the clinical profile, complications, diagnostic characteristics, and antimicrobial susceptibility patterns of typhoid fever. However, relatively limited data are available regarding the specific clinical and laboratory factors that independently predict delayed clinical recovery in children. Identifying such predictors may allow clinicians to recognize high-risk patients early, intensify monitoring, optimize supportive management, and reconsider antimicrobial therapy when clinically indicated.

Therefore, the present study was undertaken to evaluate the demographic, clinical, laboratory, microbiological, and treatment-related factors associated with delayed clinical recovery among children with typhoid fever and to identify independent predictors of delayed recovery using multivariable analysis.

Materials and Methods

Study Design and Setting: The present study was designed as a hospital-based observational study to identify the clinical, laboratory, and demographic predictors associated with delayed clinical recovery in children diagnosed with typhoid fever. The study was conducted in the Department of Pediatrics of a tertiary care teaching hospital over a period of one year.

Study Population: The study included 100 children diagnosed with typhoid fever who attended the pediatric outpatient department or were admitted to the pediatric wards during the study period. Eligible children were enrolled consecutively after fulfilling the predefined inclusion and exclusion criteria.

Inclusion Criteria

Children were eligible for inclusion if they:

- Were aged ≤18 years.
- Had a clinical diagnosis of typhoid fever supported by appropriate laboratory investigation.
- Presented during the study period.
- Had sufficient clinical and laboratory information available for assessment of recovery.
- Were willing to participate, with written informed consent obtained from the parent or legally authorized guardian.

Exclusion Criteria

Children were excluded authorised they:

- Had incomplete clinical or laboratory records.
- Had a documented chronic systemic illness likely to influence clinical recovery.
- Had a concurrent serious bacterial or viral infection.
- Had received treatment for typhoid fever before presentation for an extended period that could interfere with assessment of clinical recovery.
- Were lost to follow-up before assessment of the recovery outcome.

Sample Size: A total of 100 pediatric patients fulfilling the eligibility criteria were included in the study. The sample size was selected based on the feasibility of recruitment during the one-year study period and the expected availability of eligible pediatric typhoid fever cases.

Study Procedure: After enrolment, relevant demographic, clinical, laboratory, and treatment-related information was collected using a structured study proforma. The demographic variables included age, sex, residence, and relevant socioeconomic characteristics. Clinical variables included duration of fever before presentation, maximum recorded temperature, presenting symptoms, gastrointestinal manifestations, vomiting, diarrhea, abdominal pain, headache, hepatomegaly, splenomegaly, dehydration, and other relevant clinical findings.

Laboratory parameters including hemoglobin, total leukocyte count, differential leukocyte count, platelet count, liver function tests, and other investigations performed as part of routine clinical management were recorded. Microbiological investigations used for confirmation of typhoid fever, including blood culture and/or other institutionally accepted diagnostic tests, were also documented. Treatment-related variables such as

antibiotic therapy, time to initiation of appropriate treatment, change of antibiotic therapy, supportive treatment, and duration of hospitalization were recorded.

Assessment of Clinical Recovery: Clinical recovery was assessed during hospitalization and follow-up based on resolution of fever and improvement of the presenting clinical symptoms and general condition.

For the purpose of analysis, patients were categorized into:

- **Early clinical recovery:** patients who achieved predefined clinical recovery within the expected recovery period.
- **Delayed clinical recovery:** patients who required a longer duration than the predefined recovery period to achieve clinical recovery.

The primary outcome of the study was delayed clinical recovery in children with typhoid fever.

Predictors Evaluated: Potential predictors of delayed clinical recovery included demographic characteristics, duration of illness before presentation, severity and duration of fever, gastrointestinal symptoms, hepatosplenomegaly, dehydration, baseline hematological parameters, liver function abnormalities, microbiological findings, treatment-related factors, and duration of hospitalization. These variables were compared between children with early and delayed clinical recovery to identify factors associated with delayed recovery.

Data Collection and Management: All relevant information was recorded in a predesigned data collection proforma. Patient confidentiality was maintained throughout the study, and identifying information was not included in the final analysis. The collected data were checked for completeness before statistical analysis.

Statistical Analysis: The collected data were entered into Microsoft Excel and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on the distribution of the data. Categorical variables were presented as frequencies and percentages.

Continuous variables between the early and delayed recovery groups were compared using the Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test.

Variables showing a significant association with delayed clinical recovery on univariate analysis were considered for multivariable analysis. Multivariable logistic regression analysis was performed to identify independent predictors of delayed clinical recovery. Results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant.

Results and Observations

The present observational study included 100 children with typhoid fever who were managed in the Department of Paediatrics at a tertiary-care teaching hospital over a period of 1 year. The demographic, clinical, laboratory, microbiological, and treatment-related variables were analysed to identify factors associated with delayed clinical recovery. For analysis, the study population was divided into two groups according to the predefined clinical recovery criteria: early clinical recovery and delayed clinical recovery.

Table 1: Distribution of Study Participants According to Clinical Recovery

Clinical recovery group	Number of patients	Percentage
Early recovery	68	68.0
Delayed recovery	32	32.0
Total	100	100.0

Of the 100 children included in the study, 68 (68.0%) achieved early clinical recovery, whereas 32 (32.0%) experienced delayed clinical recovery.

Table 2: Demographic Characteristics of the Study Participants

Variable	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Age, mean ± SD (years)	8.1 ± 3.6	9.4 ± 3.8	0.09
Male, n (%)	39 (57.4)	20 (62.5)	0.63
Female, n (%)	29 (42.6)	12 (37.5)	0.63
Urban residence, n (%)	40 (58.8)	14 (43.8)	0.16
Rural residence, n (%)	28 (41.2)	18 (56.2)	0.16

There was no statistically significant difference between the early and delayed recovery groups with respect to age, sex, or place of residence.

Table 3: Clinical Characteristics of Children with Typhoid Fever

Clinical variable	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Fever duration before presentation >7 days, n (%)	17 (25.0)	17 (53.1)	0.006
High-grade fever, n (%)	31 (45.6)	22 (68.8)	0.031
Vomiting, n (%)	18 (26.5)	14 (43.8)	0.09
Diarrhea, n (%)	21 (30.9)	14 (43.8)	0.22
Abdominal pain, n (%)	20 (29.4)	15 (46.9)	0.09
Hepatomegaly, n (%)	12 (17.6)	12 (37.5)	0.025
Splenomegaly, n (%)	9 (13.2)	10 (31.3)	0.031
Dehydration, n (%)	8 (11.8)	10 (31.3)	0.020

Children with delayed recovery more frequently had a longer duration of fever before presentation, high-grade fever, hepatomegaly, splenomegaly, and dehydration. Fever duration >7 days before presentation showed a statistically significant association with delayed clinical recovery.

Table 4: Laboratory Characteristics of the Study Participants

Laboratory parameter	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Hemoglobin (g/dL), mean ± SD	11.2 ± 1.3	10.6 ± 1.4	0.03
Total leukocyte count (cells/mm³), mean ± SD	5,860 ± 1,540	5,220 ± 1,610	0.06
Platelet count (×10³/mm³), mean ± SD	208 ± 52	184 ± 61	0.04
Elevated AST, n (%)	13 (19.1)	13 (40.6)	0.024
Elevated ALT, n (%)	11 (16.2)	12 (37.5)	0.020
Elevated bilirubin, n (%)	6 (8.8)	7 (21.9)	0.08

Children with delayed recovery had lower mean hemoglobin and platelet counts compared with those who recovered early. Elevated AST and ALT levels were significantly more frequent among children with delayed recovery.

Table 5: Microbiological and Diagnostic Findings

Diagnostic variable	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Blood culture positive, n (%)	24 (35.3)	16 (50.0)	0.17
Blood culture negative, n (%)	44 (64.7)	16 (50.0)	0.17
Documented antibiotic sensitivity, n (%)	22 (32.4)	14 (43.8)	0.27
Antibiotic modification required, n (%)	7 (10.3)	9 (28.1)	0.024

Blood culture positivity was more frequent among children with delayed recovery, although the difference was not statistically significant. Requirement for modification of antibiotic therapy was significantly more common in the delayed recovery group.

Table 6: Treatment-Related Characteristics

Treatment variable	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Appropriate antibiotic started within 48 h, n (%)	57 (83.8)	21 (65.6)	0.043
Antibiotic modification required, n (%)	7 (10.3)	9 (28.1)	0.024
Supportive IV fluid therapy, n (%)	15 (22.1)	14 (43.8)	0.026
Hospital stay >7 days, n (%)	8 (11.8)	17 (53.1)	<0.001

Delayed recovery was significantly associated with later initiation of appropriate antibiotic therapy, requirement for antibiotic modification, need for intravenous fluid therapy, and prolonged hospitalization.

Table 7: Comparison of Duration of Clinical Recovery

Outcome	Early recovery (n=68)	Delayed recovery (n=32)	p-value
Duration to clinical recovery (days), mean ± SD	4.8 ± 1.2	9.1 ± 2.4	<0.001
Hospital stay (days), mean ± SD	5.2 ± 1.5	9.4 ± 3.0	<0.001

The mean duration to clinical recovery was substantially higher among children classified as having delayed recovery. Similarly, children with delayed recovery had a significantly longer duration of hospitalization.

Table 8: Univariate Analysis of Potential Predictors of Delayed Clinical Recovery

Potential predictor	Odds Ratio (OR)	95% CI	p-value
Fever >7 days before presentation	3.38	1.39–8.21	0.007
High-grade fever	2.63	1.07–6.47	0.035
Hepatomegaly	2.81	1.06–7.43	0.038
Splenomegaly	2.99	1.02–8.73	0.046
Dehydration	3.41	1.16–10.02	0.026
Elevated AST	2.88	1.13–7.34	0.027
Elevated ALT	3.11	1.18–8.19	0.021
Antibiotic modification	3.40	1.20–9.65	0.021

On univariate analysis, prolonged fever before presentation, high-grade fever, hepatomegaly, splenomegaly, dehydration, elevated liver enzymes, and requirement for antibiotic modification were associated with increased odds of delayed clinical recovery.

Table 9: Multivariable Logistic Regression Analysis of Independent Predictors

Predictor	Adjusted OR	95% CI	p-value
Fever >7 days before presentation	3.02	1.18–7.73	0.020
Dehydration	2.91	1.01–8.38	0.048
Elevated ALT	2.76	1.04–7.34	0.042
Hepatomegaly	2.31	0.86–6.18	0.094
Splenomegaly	2.17	0.75–6.28	0.153
Antibiotic modification	2.89	1.02–8.18	0.046

Multivariable logistic regression identified fever lasting >7 days before presentation, dehydration, elevated ALT, and requirement for antibiotic modification as independent predictors of delayed clinical recovery.

Discussion

The present hospital-based observational study evaluated 100 children with typhoid fever and assessed demographic, clinical, laboratory, microbiological, and treatment-related factors associated with delayed clinical recovery. In the present study, 68% of children achieved early clinical recovery, whereas 32% experienced delayed recovery. The analysis demonstrated that prolonged fever before presentation, dehydration, elevated ALT, and requirement for antibiotic modification were independent predictors of delayed clinical recovery.

In the present study, demographic variables including age, sex, and place of residence were not significantly associated with delayed recovery. Although children in the delayed recovery group had a slightly higher mean age than those in the early recovery group, the difference was not statistically significant. Similarly, there was no significant association between sex or urban/rural residence and recovery status. These findings suggest that clinical severity and timing of presentation may be more important determinants of recovery than basic demographic characteristics. Previous studies have also demonstrated considerable variability in the clinical presentation of enteric fever across different pediatric populations [3,4].

A significant association was observed between fever duration of more than 7 days before presentation and delayed clinical recovery. Children presenting after more than 7 days of fever had more than threefold higher odds of delayed recovery on univariate analysis, and this association remained significant after multivariable adjustment. Prolonged untreated infection may allow progressive systemic involvement and increase the likelihood of complications or persistent symptoms. Delayed initiation of appropriate therapy has been recognized as an important factor contributing to increased morbidity in enteric fever [6,10]. The present finding therefore emphasizes the importance of early diagnosis and treatment.

High-grade fever was significantly more common among children with delayed recovery on univariate analysis. However, it did not remain an independent predictor after adjustment for other factors. Fever is the most common clinical manifestation of typhoid fever and may persist for several days even after initiation of therapy [3,6]. High-grade or persistent fever may reflect a greater disease burden, but its effect may be mediated through other indicators of severity such as prolonged illness and dehydration. Hepatomegaly and splenomegaly were significantly more frequent among children with delayed recovery. However, neither remained statistically significant in the multivariable model. Hepatosplenomegaly is a recognized manifestation of enteric fever and may reflect systemic reticuloendothelial involvement [3,5]. The loss of significance following adjustment suggests that these clinical findings may be associated with other markers of disease severity rather than acting as independent determinants of delayed recovery.

Dehydration emerged as an independent predictor of delayed clinical recovery in the present study. Children with dehydration had approximately three times greater adjusted odds of delayed recovery. Dehydration may result from prolonged fever, inadequate oral intake, vomiting, diarrhea, or increased fluid requirements during systemic infection. It may further compromise the child's general condition and delay clinical improvement. Adequate fluid and electrolyte management is therefore an important component of supportive care in pediatric enteric fever [6,11].

The laboratory findings demonstrated significantly lower mean hemoglobin and platelet counts among children with delayed recovery. Although these variables were not retained as independent predictors, their association may indicate greater systemic involvement. Hematological abnormalities, particularly thrombocytopenia, have been described in children with enteric fever and may vary according to disease severity and duration [4,5]. The total leukocyte count was also lower in the delayed recovery group, although the difference did not reach statistical significance.

A significant association was observed between elevated liver enzymes and delayed recovery. Elevated AST and ALT were more frequent among children with delayed recovery. Importantly, elevated ALT remained an independent predictor after multivariable adjustment, with an adjusted odds ratio of 2.76. Hepatic involvement is a recognized complication or manifestation of enteric fever, ranging from mild elevation of aminotransferases to clinically significant hepatitis [5,12]. The association between elevated ALT and delayed recovery in the present study may indicate greater systemic or hepatic involvement and may serve as a useful marker of children requiring closer monitoring.

Blood culture positivity was more frequent in the delayed recovery group, although the difference was not statistically significant. Blood culture remains an important diagnostic method for enteric fever; however, its sensitivity may be affected by prior antibiotic exposure, timing of sample collection, and bacterial load [2,6]. Therefore, culture positivity alone may not reliably predict clinical recovery. The absence of a significant association in the present study suggests that clinical and biochemical indicators may provide additional information regarding expected recovery.

The requirement for antibiotic modification was significantly associated with delayed recovery and remained an independent predictor in the multivariable analysis. Children requiring modification of antibiotic therapy had nearly three times higher adjusted odds of delayed recovery. Antibiotic modification may indicate inadequate response to initial therapy, antimicrobial resistance, intolerance, or clinical deterioration. The increasing prevalence of antimicrobial resistance in *S. Typhi* has become a major challenge in the treatment of enteric fever, particularly in South Asia [8,9]. Extensively drug-resistant typhoid has further emphasized the importance of appropriate antimicrobial selection and susceptibility-guided treatment whenever possible [9].

Timely initiation of appropriate antibiotic therapy was significantly more common among children who achieved early recovery. In the present study, 83.8% of children in the early recovery group received appropriate antibiotics within 48 hours compared with 65.6% in the delayed recovery group. Although this variable was not retained as an independent predictor in the final regression model, the finding supports the importance of early effective treatment. Appropriate antimicrobial therapy is known to shorten the duration of illness and reduce the risk of complications associated with enteric fever [6,10].

Supportive intravenous fluid therapy was significantly more frequent among children with delayed recovery. This finding is likely related to the higher prevalence of dehydration and more severe clinical manifestations in this group. Similarly, children with delayed recovery had significantly longer hospital stays. The mean duration of hospitalization was 9.4 days in the delayed recovery group compared with 5.2 days in the early recovery group. Prolonged hospitalization is clinically important because it increases healthcare utilization and may reflect greater disease severity.

The multivariable logistic regression analysis identified four independent predictors of delayed clinical recovery: fever >7 days before presentation, dehydration, elevated ALT, and antibiotic modification. Among these, prolonged fever before presentation had an adjusted OR of 3.02, dehydration had an adjusted OR of 2.91, elevated ALT had an adjusted OR of 2.76, and antibiotic modification had an adjusted OR of 2.89. These findings indicate that delayed presentation, compromised hydration, hepatic involvement, and inadequate or ineffective initial antimicrobial therapy are particularly important factors associated with prolonged recovery.

The findings have important clinical implications. Children presenting with prolonged fever should be carefully assessed for disease severity and complications. Hydration status should be evaluated promptly, and dehydration should be corrected appropriately. Baseline liver function testing may help identify children with hepatic involvement who may require closer observation.

In addition, failure to respond adequately to initial antimicrobial therapy should prompt reassessment of diagnosis, treatment adherence, antimicrobial susceptibility, and the possibility of resistant infection.

The present study has several limitations. It was conducted at a single tertiary care teaching hospital and included a relatively small sample of 100 children, which may limit generalizability. The observational design does not permit definite conclusions regarding causality. Some treatment-related variables may also have been influenced by individual clinician judgment and local antimicrobial practices. Furthermore, the study population consisted of hospital-attending children and may therefore not represent all children with typhoid fever in the community. Larger prospective multicentric studies are required to validate these predictors and develop a reliable clinical prediction model.

Despite these limitations, the study provides useful evidence regarding factors associated with delayed recovery in pediatric typhoid fever. Prolonged fever before presentation, dehydration, elevated ALT, and requirement for antibiotic modification were identified as independent predictors of delayed clinical recovery. Recognition of these factors at the time of presentation may assist clinicians in identifying children at increased risk of prolonged illness and facilitate timely supportive and antimicrobial management.

Conclusion

Delayed clinical recovery was observed in 32% of children with typhoid fever. Prolonged fever before presentation, dehydration, elevated ALT, and requirement for antibiotic modification were identified as independent predictors of delayed recovery. Early recognition of these factors may facilitate timely treatment, closer monitoring, and appropriate supportive care, thereby improving clinical outcomes in pediatric typhoid fever.

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