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The Relationship Between CRP Level and Age in Salmonella Typhi Patient

Haider Abdul-Moneem Al-Mothafer[1]

[1]*Anesthesia Techniques Department, College of Health & Medical Techniques / Kufa, Al-Furat Al-Awsat Technical University, Iraq*

**Corresponding Author: Haider Abdul-Moneem Al-Mothafer*
Email: haider.mohamed.chm@atu.edu.iq

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Abstract

Typhoid fever has increased in some populations, hence the current study, aimed to evaluate the prevalence of salmonella seropositivity and other relevant factors such as sex, age, and CRP positivity among febrile patients, especially among the patients estimated to be suffering with typhoid fever located at Al-Najaf province in Iraq. The study comprised 79 febrile patients who presented for intestinal complaints at Al-Hakeem General Hospital, AL Sajad Hospital, and AL Najaf Hospital's serological departments within Al-Najaf province between October 2024 and January 2025. Those were between 1 and 75 years of age. This study employed rapid testing modalities for the qualitative detection of typhoid infection and assessment of serum CRP levels. Among the 79 febrile patients screened, 41 (51.9%) were female, 38 male (48.1%) was assessed. On typhoid seropositivity, 23 individuals (29.2%) tested positive, and 56 (70.8%) negative, but no differences between gender were found (P=0.36). Age distribution of febrile patients was further classified into 5 groups, 1-15 years, 16-30 years, 31-45 years, 46-60 years, 61-75 years. Notably, the greatest prevalence occurred at a range of 1 to 15 years of age (27.8%), then in the 16-30 year group (25.3%). Among those diagnosed as positive for Salmonella seropositivity, it was reported that those ages 61-75 had a higher positivity rate of 12.7%, indicating a statistically significant difference (P=0.001).

Introduction

Typhoid fever, often referred to as enteric fever, is a prevalent illness found in many countries, primarily resulting from the bacterium *Salmonella typhi*, while *Salmonella enterica* serovars Paratyphi (S. Paratyphi) rank as the second most frequent pathogen involved. Humans are the exclusive host for this bacterium (Aljanaby and Medhat, 2017; Teferi et al., 2021). Annually, millions of individuals become infected with typhoid fever, rendering it a major public health issue in low-income regions, especially throughout East and West Asia (Galgallo et al., 2018).

Salmonella typhi is identified as a Gram-negative bacterium characterized by its motility, which is attributed to peritrichous flagella. It has a positive reaction for hydrogen sulfide (H2S) and forms black colonies on SS-agar plates (Masuet-Aumatell and Atouguia, 2021). The main pathways for transmission involve consumption of food and water contaminated with S. typhi (Brockett et al., 2020). This pathogen can impact the intestinal system as well as the bloodstream or penetrate multiple organs while releasing endotoxins. It remains a persistent issue in developing regions and is increasingly demonstrating resistance to various commonly used antimicrobial treatments (Nassir et al., 2024). In patients infected with Salmonella typhi, there is a significant rise in levels of the acute phase protein C-reactive protein (CRP), leading to its adoption as a diagnostic marker for acute enteric fever infections (Ayyoub et al., 2022).

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Incidence rates play a crucial role in informing strategic choices regarding the allocation of limited resources for controlling and preventing infectious diseases. By implementing prospective surveillance on patients exhibiting an undifferentiated febrile syndrome, it is possible to obtain a more accurate assessment of the disease burden associated with typhoid (Srikantiah et al., 200). There have been numerous studies both within Iraq and internationally that have investigated typhoid fever, revealing differing results concerning its prevalence in relation to demographics such as population, gender, age, and CRP levels. Consequently, the present study seeks to assess the incidence of typhoid fever in AL-Najaf and explore its association with age, sex, and CRP positivity through the following objectives:

Aim of the study

Determination of the more susceptible age group typhoid fever patients and Determination CRP seropositivity in febrile patients and type of typhoid fever (acute or chronic) by CRP.

Typhoid Fever

Typhoid fever is a serious bacterial infection that significantly impacts public health, particularly in Africa and Asia. This disease predominantly affects people from infancy to young adulthood. The responsible pathogen, *Salmonella enterica subsp. Enterica serovar Typhi*, spreads through the fecal-oral route, infiltrating the intestinal lining and spreading to systemic and intracellular locations, leading to a nonspecific febrile illness. Blood cultures are still the most reliable technique for diagnosing typhoid fever when available. but novel diagnostic approaches are an important part of current research. The prevalence of both typhoid fever and antimicrobial resistance has been evaluated at global level since 2017. Furthermore, advancement in understanding disease correlates and immunological defense via controlled human infection studies, as well as efforts to improve vaccine-effectiveness through collaborative activity among various partners and targeted clinical trials in a range of high-incidence regions, has been achieved. This Primer therefore serves as a timely update on these advances as well as future priorities for the global scientific community (Meiring et al., 2023).

The typhoid bacillus produces a mild, diffusible toxin that is produced both in the intestinal tract and within the bloodstream as well as other organs. This toxin induces the proliferation of endothelial cells, thereby causing the endothelial cells to become malignant for some period of time. The newly forming cells have an epithelioid nature with irregular, lightly stained, eccentrically arranged nuclei and abundant, clearly defined acidophilic protoplasm. Moreover, these cells have remarkable phagocytic properties. The highest concentration of these phagocytic cells is found along the absorption line in the intestinal tract (Mallory, 1898)

Complications of Typhoid Fever

Marchello et al. (2020) categorize the complications associated with typhoid fever into several distinct groups:

Abdominal Complications: These include intestinal perforation, gastrointestinal bleeding, hepatitis, and cholecystitis.

Cardiovascular Issues: This category encompasses asymptomatic changes in electrocardiograms, myocarditis, and shock.

Neuropsychiatric Complications: This includes conditions such as encephalopathy, delirium, psychotic episodes, meningitis, and issues related to coordination.

Respiratory Complications: Primarily bronchitis and pneumonia fall under this classification.

Hematologic Issues: Anemia and disseminated intravascular coagulation are noted here.

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Additional Complications: This group covers focal abscesses, pharyngitis, miscarriages, relapses of the disease, chronic bacterial carriage, as well as seizures or convulsions.

Salmonellae

The prevalence of Salmonella species (spp.) in different environments is mainly because of the high abundance in the intestinal tracts of animals with similar types of bacteria (Lauteri et al., 2022). Humans typically contract these bacteria through contaminated food and water (Prasertsee et al., 2022). Salmonella was initially identified in the 1800s (Merchant, 1969), and it was successfully cultured by Salmon and Smith in 1888 (Bryan et al., 1979). The first documented case and isolation in humans also occurred in that same year, reported by Gartner. A total of approximately 1600 Salmonella serotypes have been identified by White Kauffmann-Le Minor, with many belonging to the subspecies enterica (Elnekave et al., 2020). More than 200 of these serotypes have been recognized as capable of causing illness in humans (Xu et al., 2021).

The *Salmonella spp.* are classified under the family *Enterobacteriaceae*. These organisms are characterized as Gram-negative and rod-shaped (WHO, 2018). According to the Kauffmann-White scheme, the genus includes two species: *Salmonella enterica* (S. enterica) and *S. bongori* (Popoff, 1997; Dione et al., 2011). Other classifications have been established based on biochemical characteristics of specific strains such as *S. Cholerasuis*, *S. Typhi*, and *S. Enteritidis* (Carter, 2004), as well as their host affinities. For example, *S. Typhi* and *S. Paratyphi* are particularly adapted to humans, whereas different species of Salmonella have evolved to thrive in specific animals: *S. Cholerasuis* is linked to swine, while both *S. Pullorum* and *S. Gallinarum* are associated with poultry, and *S. Dublin* is connected to cattle. Furthermore, some Salmonella species do not exhibit a preference for any particular host (Rahman, 2017).

Worldwide, foodborne diseases associated with Salmonella have posed a considerable public health challenge for over a hundred years (Worku et al., 2022). These illnesses related to Salmonella are divided into two categories: typhoidal salmonellosis (TS), also referred to as enteric fever, and non-typhoidal Salmonella (NTS) infections (Akinyemi et al., 2021). Typhoid fever is attributed to Salmonella enterica serovar Typhi, while the paratyphoid fever, which exclusively affects humans, is caused by S. Paratyphi A, B, and C. NTS infections originate from various serovars of S. enterica (Ngogo et al., 2020). Key serovars such as Salmonella Enteritidis, S. Choleraesuis, and S. Typhimurium contribute to human illness through the contamination of food products that serve as primary reservoirs for these bacteria (Thung et al., 2018). Invasive typhoidal salmonellosis is characterized by symptoms such as enteric fever, gastroenteritis, and bacteremia. In contrast, non-typhoidal salmonellosis primarily presents as gastroenteritis, with common symptoms including diarrhea, abdominal cramps, and vomiting that primarily affect the ileum and colon (Gong et al., 2022). This research seeks to delineate the features, classification, naming conventions, and fundamental properties of Salmonella while offering a comprehensive overview of both non-typhoidal (NTS) and typhoidal salmonellosis (TS). The Salmonella genus falls under the Enterobacteriaceae family; these bacteria are Gram-negative and yield negative results in the oxidase test. They possess motility due to peritrichous flagella, have a rod-shaped structure, do not form spores, and are categorized as facultative anaerobes (Lertworapreecha et al., 2013).

The dimensions of Salmonella species are typically around 2-3 x 0.4-0.6 μm (Yousef, 2003; Montville, 2008). Generally, Salmonella produces hydrogen sulfide and metabolizes D-glucose to generate hydrogen and carbon dioxide while converting nitrates into nitrites (Pui et al., 2011). Almost all Salmonella serovars can produce gas, with the exception of Salmonella

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serovar Typhimurium, which is unable to do so (Popoff, 2005). These bacteria yield negative results for urease and indole (tryptophanase) production. According to the sequence analysis of the 16S rDNA gene, Salmonella is categorized within the Gamma proteobacteria class (Cosby et al., 2015). The composition of Salmonella's cell wall includes lipids, lipopolysaccharides, proteins, and lipoproteins. Additionally, the polysaccharides and monosaccharides linked to the endotoxin are commonly known as somatic O antigens (Yavari, 2012).

Salmonella virulence factors

The elements that contribute to virulence play a critical role at different points during an infection. These factors include the synthesis of toxins such as LPS endotoxin, enterotoxin, and cytotoxin as well as mechanisms like colonization, adhesion, invasion, and the capacity to survive within host cells (Madigan, 2007). The Vi antigen located in the capsule consists of a linear homopolymer formed by α-1–4 linked galactose aminouronic acid and exhibits variations in acetylation at the C3 position. This antigen is associated with both SPI-1 and SPI-2 along with type III secretion systems. Both typhoidal and non-typhoidal Salmonella species contain two pathogenicity islands that encode Type III secretion systems (T3SS): SPI-1 and SPI-2 T3SS, which are vital for the virulence of Salmonella. In S. Typhi specifically, the SPI-1 T3SS is particularly crucial for penetrating non-phagocytic cells (Robbins, 1984).

Somatic O Antigen (Cell Wall Ag or LPS)

Below the capsular layer is an outer L-layer including lipopolysaccharide (LPS), commonly called the ‘O’ antigen. The outer membrane proteins (OMP), which possess antigenic properties, are included in this layer. The OMPs consist of porins (such as OMP F and OMP C) as well as other non-porin constituents. Porins act as the solute uptake channels whereas non-porin proteins are structural (Bishop, 2008).

Flagella (H Antigen)

Not only do flagella enhance virulence, but they also have a role in generating innate immune reactions through the detection of monomeric flagellin by TLR5 and NAIP receptors (Benz, 1988; Hayashi et al., 2001).

Fimbriae and pili

Act as adhesion factors. Such virulence components are involved as mediators in infection and are needed for host colonization, and for their interaction with host cells (Kortmann et al., 2015). Though certain Salmonella strains harbor large plasmids with low copy numbers of the virulence genes required to affect systemic disease, their exact role within the enteric part of infection is unknown. While these virulence plasmids differ in size (50–90 kb), they all have a critical region, 7.8 kb (SPV), essential for bacterial proliferation in the reticuloendothelial system (Berrocal, 2015; Safia Sultana, 2012).

***Salmonellae typhi* diagnosis**

Similarly, the lack of specificity in rapid diagnostic tests (RDTs) for typhoid fever poses a risk of misdiagnosis, which may lead to unnecessary antibiotic prescriptions and delays in receiving appropriate treatment for the actual underlying conditions. For example, during an outbreak of acute febrile illness in Nepal, the Widal test was utilized, resulting in incorrect identification of typhoid fever and postponing treatment for the actual cause, which was scrub typhus, ultimately leading to numerous fatalities (Basnyat, 2016). Although RDTs are widely accessible, cost-effective, and user-friendly, they contribute to an increased likelihood of

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misdiagnosing typhoid fever (Schroeder et al., 2022). Additionally, the bacterium Salmonella Typhi possesses biological characteristics that complicate laboratory diagnosis. It can circumvent the gastrointestinal mucosal barrier that typically limits other enteric pathogens, avoid standard innate immune defenses, and elicit minimal inflammatory responses (Raffatellu et al., 2008). S. Typhi infection is believed to begin with its invasion of the mucosa in the terminal ileum; these bacteria are thought to exist only briefly in the bloodstream before disseminating throughout the reticuloendothelial system and have been shown to infect various organs including the bone marrow, liver, and spleen (Baker et al., 2010).

Bacterial loads in peripheral blood are the highest in the first week of illness (Wain et al., 1998), but their intensity remains relatively small, with a median CFU/mL of 0.1−1.0 observed in symptomatic patients (Khanam et al., 2013). Such concentration is very low indeed and is too small to be detected through blood cultures or PCR methods, and therefore, these diagnostic methods become less sensitive. Salmonella Typhi is a member of the Enterobacteriaceae family and exhibits cross-reactivity with antibodies generated from prior infections with other members of this family, due to the strong conservation of its surface antigens. This cross-reactivity undermines the reliability of antibody-based diagnostic tests, which, aside from their cost implications, have the potential for providing quick and cost-effective screening. Additionally, an invasive typhoid infection is confirmed through the isolation of S. Typhi from blood cultures; however, this approach is costly, takes more than 48 hours for results, has lower sensitivity, and generally necessitates laboratory facilities and trained personnel resources that are often scarce in low- and middle-income countries (LMIC) where typhoid fever is prevalent (Von Kalckreuth et al., 2016).

Typhoid Rapid Test

Typhoid fever can be by typhoid rapid test:

The typhoid rapid test, also known as the typhoid serology test or the Widal test, is used to diagnose typhoid fever, a systemic illness caused by the bacterium Salmonella enterica serotype Typhi (Willke *et al* ., 2002).

Unlike the Rose Bengal test, which detects antibodies, the typhoid rapid test primarily detects antibodies (particularly IgM and IgG) against specific antigens of Salmonella Typhi (Díaz *et al*., 2011).

This test involves mixing the patient's serum with antigens from Salmonella Typhi and observing for agglutination reactions (Wijedoru *et al*., 2017).

Interpretation of the test results involves measuring the agglutination pattern and titers of antibodies, which can provide information about the stage of the infection and the patient's immune response (Andualem et al., 2014).

While the typhoid rapid test can provide quick results, it may not be as sensitive or specific as other diagnostic methods, such as blood culture or polymerase chain reaction (PCR) assays (Najib, 2021).

C-Reactive Protein:

C-reactive protein (CRP) is a protein in plasma that has remained highly conserved throughout evolution, in vertebrates in addition to many invertebrates. It participates in the body’s systemic response to inflammation. The plasma concentration of CRP during inflammatory conditions increases dramatically and this property has been used clinically for many years. CRP operates as a pattern recognition molecule, binding to specific molecular structures which are normally

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unveiled at cellular death or are hosted on the surfaces of pathogens. Rapidly occurring in hours after tissue damage or infection, the high synthesis of CRP implicates its activity for host defense mechanisms and further implies its function in the innate immune response (Black et al., 2004). C-reactive protein (CRP) is a polypeptide classified within the pentraxin family. It has a molecular weight of 120,000 daltons and consists of five identical subunits, each made up of 206 amino acids. The liver is the primary site for CRP synthesis, which occurs in response to certain pro-inflammatory cytokines. This protein plays an essential role in innate immunity, aiding in opsonization due to its inherent properties, as well as complement activation and interaction with immunoglobulin receptors. Serving as a significant marker for acute systemic inflammation, CRP is an important indicator of inflammatory processes (Moutachakkir et al., 2017).

The CRP plays an important role in vivo in host defense against salmonellae during the early stages of infection (Szalai et al., 2000), but can no used as a single screening test to distinguish between *Salmonella* and nonbacterial gastroenteritis (Meloni et al., 1999).

Methods

Collection of Specimens

From October 2024 to January 2025, a total of 79 febrile patients experiencing intestinal issues were assessed. These individuals sought care at the serological department of Al-Hakeem General Hospital, AL Sajad Hospital, and AL Najaf Hospital, all located in the province of AL-Najaf, Iraq. The ages of the patients with hypertension varied between 1 and 75 years.

Blood Samples

Blood from patients was collected, centrifuged, and serums used to detect Salmonella were obtained.

Experimental Study Design

The design of this study is summarized in figure 1.

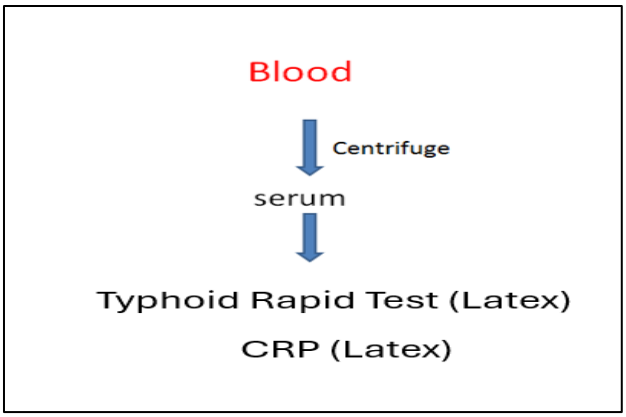

Figure 1. Flow chart illustrating the experimental study design.

Salmonella Diagnosis

Salmonella was identified through serological testing using the Rapid test (ENTEROCHECK –WB, Tulip Diagnostic LTD, India), as illustrated in figure (3-2), following the guidelines provided by the manufacturer.

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Testing Procedure and Result Interpretation

Before the test procedure was initiated, all components of the ENTEROCHECK® WB kit were allowed to reach room temperature. The foil pouch was then opened carefully at the designated notch area. After opening the package, the testing device and desiccant pouch were removed and inspected. The desiccant color was checked to ensure the validity of the device. A blue desiccant indicated that the device was suitable for use, whereas a colorless or pink desiccant indicated that the device should be discarded and replaced with a new one. The testing device was used immediately after opening the package.

Next, the testing device was labeled with the appropriate specimen identification to avoid sample misinterpretation. The device was then placed on a stable and flat surface. Using a micropipette, 5 µl of whole blood, serum, or plasma was carefully dispensed into specimen port A. Alternatively, the sample applicator provided in the kit could be used by dipping it into the specimen and gently applying the sample onto specimen port A.

Following sample application, five drops of sample running buffer were added into buffer port B. The device was then left undisturbed to allow the reaction process to occur properly. The test results were observed and interpreted after 15 minutes.

C-Reactive Protein

Procedure (Qualitative Method)

Allow the reagents and samples to acclimate to room temperature, as lower temperatures can reduce the sensitivity of the test.

Dispense 50 µL of the sample (Note 1) and one drop each of Positive and Negative controls into separate designated circles on the test slide.

Prior to use, ensure that the CRP-latex reagent is well mixed either manually or using a vortex mixer, then add a drop (50 µL) adjacent to the samples being tested.

Utilize a stirrer to thoroughly blend the drops, ensuring even distribution across each circle's surface; make sure to use separate stirrers for each sample.

Position the slide on a mechanical rotator set at 80-100 r.p.m. for a duration of 2 minutes; any delay in reading beyond this time frame may result in false positive outcomes in test results.

Reagents

Latex	Latex particles are treated with goat IgG antibodies against human CRP at a pH of 8.2.
Control + Red cap	Human serum exhibiting a CRP concentration exceeding 20 mg/L, containing a preservative.
Control- Blue cap	Serum derived from animals, also containing a preservative.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 26. The Chi-square test was employed to test for significant differences in qualitative outcomes among the various groups. Statistical significance levels $P \leq 0.05$ were applied (Cesana, 2018).

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Results and Discussion

The age span of febrile patients in this study ranges from 1 to 75 years. Five age groups were identified as participants: 1-15, 16-30, 31-45, 46-60, and 61-75 years. The age category with the highest prevalence of fever is that of 1-15 years (27.8%), closely followed by 16-30 years old (25.3%). Nevertheless with respect to Salmonella seropositivity, the age group of 61-75 years shows the highest positivity rate at 12.7% with statistically significant differences (P=0.001) as shown in Table 1.

Table1. Distribution of febrile patients based on salmonella seropositivity and age categories

Age Group	Positive	%	Negative	%	Febrile	%
1-15	3	3.8	19	24.0	22	27.8
16-30	1	1.3	19	24.0	20	25.3
31-45	5	6.3	8	10.1	13	16.4
46-60	4	5.1	6	7.6	10	12.7
61-75	10	12.7	4	5.1	14	17.8
Total	23	29.2	56	70.8	79	100

The age group most susceptible to febrile diseases is 1–15 years, which is 27.8% of the overall study population, and this is followed by people aged 16–30 years. In stark contrast, the age range most vulnerable to typhoid fever is 61–75 years, with a susceptibility rate of 12.7%. Kumar et al. (2013) revealed that infections were greatest among people aged 11–20 years, then 21–30 years. Conversely, Allu et al. (2019) identified the age group 21–30 as specifically being at risk of typhoid fever. Differences in study designs or populations might also explain differences observed in findings or case distributions.

This study used a rapid test for qualitative detection of typhoid infection and serum CRP levels (positive or negative). In the present study, 23 (29.2%) of febrile patients had the CRP positive result, 5.1% (4) of Salmonella-positive febrile patients had the CRP positive result. The difference between these demographics was insignificant (P=0.14, see Table 4-3).

Table 2. Analysis of febrile patients based on CRP seropositivity and typhoid fever incidence

Typhoid Fever	CRP				Febrile	
	positive		Negative			
	No	%	No	%	No	%
Positive	6	7.6	22	27.8	18	22.8
Negative	17	21.5	34	43	61	77.2
Total	23	29.2	56	70.8	79	100

A non-significant relationship between CRP levels and typhoid seropositivity in fever was found (P=0.14). Zhang et al. (2021) showed that CRP levels in people with Salmonella-related gastroenteritis were higher than in their counterparts infected with viral pathogens including rotavirus. This result shows that CRP can be a helpful marker to differentiate bacterial from viral infections in the gastrointestinal tract. Other diagnostic methods, though, are still necessary for precise pathogen identification. Additionally, Oliveira et al. (2022) showed that the CRP levels among patients infected with severe systemic Salmonella were significantly higher than those with self-limiting gastroenteritis.

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Conclusion

The Index of typhoid fever is 29.2%, 1–15 year is its more affect febrile age group. The Seropositive age Group which is more Salmonellae, 61-75 years. Women have much higher CRP seropositivity.

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