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Phenotypic and potential virulence features of *Salmonella enterica* serotypes from cancer patients in Kolkata, India

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Abstract

Background *Salmonella enterica* is a leading cause of gastroenteritis and enteric fever. In this study, we sought to investigate the phenotypic and genotypic characteristics of *S. enterica* isolated from the cancer patients admitted at the Tata Medical Center, Kolkata over a period of eight years (2016–2023).

Methods *Salmonella enterica* isolates were identified by standard biochemical and serotyping. Antimicrobial susceptibility was tested by disk diffusion method and virulence genes were identified by PCR. The genetic relatedness of strains was determined by pulsed-field gel electrophoresis (PFGE) methods.

Results A total of 122 *S. enterica* isolates were identified and classified into 18 different serovars. *S.* Typhimurium (28.7%), *S.* Kentucky (22.1%), *S.* Enteritidis (13.9%), *S.* Typhi (5.7%) and *S.* Agona (5.7%) were identified as the common serovars. *S. enterica* infection was more often detected in adults (77.9%) than in children of 6–18 years old (11.4%) and < 5 years of age (10.6%). The maximum number of *S.* enterica was isolated from blood (52.4%) followed by those isolated from stool (36.9%) and urine (5.7%). *S.* enterica infections were detected among patients with chronic myelogenous leukemia (CML)/acute lymphoblastic leukemia (ALL) (24.6%) than Hodgkin lymphoma/non-Hodgkin lymphoma (16.4%), multiple myeloma (9.8%), lung adenocarcinoma (9%), prostate adenocarcinoma (6.6%), and endometrium carcinoma (5.7%). *S.* Kentucky showed a statistically significant association with hematologic malignancies ($p < 0.001$), whereas *S.* Enteritidis was significantly present in Hodgkin lymphoma and acute lymphoblastic leukemia/Chronic myelogenous leukemia cancer types ($p = 0.004$). Most of the *S. enterica* isolates displayed resistance to erythromycin (62.9%), nalidixic acid (62.9%) and tetracycline (33.9%). *Salmonella* pathogenicity island (SPI)-associated genes (*orgA*, *ssaQ*, *misL*, *invE/A*, *spi4D*, *pipA and ttrc*) were uniformly present in majority of the isolates. The hyper invasive locus (*hilA*), *Salmonella* enterotoxin (*stn*), *Salmonella* outer protein (*sopB*), virulence plasmid (*spvC*), and plasmid encoded fimbriae (*pefA*) genes were present in 76%, 69%, 51%, 32% and 17% of the isolates, respectively. Clonal analysis of the representative homologous serovars using pulsed-field gel electrophoresis revealed specific clusters with 40 to 90% similarity within each serotype.

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Conclusions Cancer patients are at increased risk of morbidity due to secondary infections, like *S. enterica*. Continuous monitoring of antimicrobial resistance patterns and virulence gene profiles in *S. enterica* isolates from this vulnerable group is critical to guide clinical management and treatment strategies.

Keywords *Salmonella enterica*, Cancer, Virulence, Antimicrobial resistance, PFGE

Introduction

Salmonella enterica is a Gram-negative bacterium and a leading cause of gastroenteritis, bacteremia, enteric fever (typhoid and paratyphoid fever) contributing substantially to global morbidity and mortality [1]. *Salmonella enterica* is classified into typhoidal *Salmonella enterica* (TS), comprising *S.* Typhi and *S.* Paratyphi A, B, and C, which cause typhoid fever in humans and non-typhoidal *Salmonella* (NTS), which includes more than 2,600 identified serotypes isolated from animals, diarrheal outbreaks, and sporadic human gastroenteritis [2]. NTS infections range from mild self-limiting gastroenteritis to severe invasive disease, particularly in immunocompromised individuals such as cancer and HIV patients. According to the World Health Organization (WHO), typhoid fever accounts for an estimated 9 million cases and 110,000 deaths globally each year [3]. Additionally, different NTS serotypes are responsible for approximately 93 million infections and 155,000 deaths annually worldwide [4].

The updated WHO Bacterial Priority Pathogens List, 2024 includes *Salmonella* Typhi and Non-Typhoidal *Salmonella* (NTS) in the “High Group” due to resistance to fluoroquinolones and third-generation cephalosporins [5]. Fluoroquinolone resistance is associated with several factors, including mutations in bacterial DNA gyrase (GyrA) and topoisomerase IV (ParA, ParC), increased efflux pump activity, and the emergence of plasmid-mediated quinolone resistance (PMQR). Third-generation cephalosporin resistance in *Salmonella* is due to the production of extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases, often carried on plasmids. These machineries can result independently or in combination, leading to a spectrum of antimicrobial resistance (AMR) levels. To quote WHO, the High Group implies antibiotic resistant bacterial pathogens that are considerably challenging to treat, cause a significant disease burden (mortality and morbidity), show increasing trends in resistance, are exceptionally difficult to prevent, are highly transmissible and for which there are few possible treatments in the development pipeline [6]. Although they may not be dangerous globally, pathogens in this category could be critical for some populations and in specific geographic areas due to a combination of environmental, socioeconomic, food and cultural factors. These factors influence the survival and spread of *Salmonella*, as well as the likelihood of human exposure and infection.

The salmonellosis is mainly transmitted by contaminated water and food of animal origin (i.e. eggs, meat, dairy products), and is facilitated by conditions characterized by poor hygiene [7]. Typhoid fever can cause life-threatening complications like intestinal hemorrhage, intestinal perforation, cerebral abscess formation and toxic myocarditis. Typhoid fever, which has high incidence rates and significant mortality, is still a major public health concern in low- and middle-income countries (LMICs), including India. The disease is particularly prevalent in India, where estimates indicate millions of cases (about 10 million cases in 2021) occur each year. Poverty, poor sanitation, and contaminated water sources are all strongly associated with this burden [8]. Most patients infected with NTS have self-limiting gastroenteritis with fever, nausea, vomiting, and abdominal pain. However, about 5–10% encounter an invasive disease that results in bacteremia and systemic complications [9]. Among NTS-associated infections, *S. enterica* serovar Typhimurium, Kentucky and Enteritidis are identified as common pathogens, especially in the South and Southeast Asian regions [10]. The serovars circulating in Asian regions are more virulent and human-adapted than the ones that have been found in developed or high-income countries. In addition, these serovars frequently carry different antimicrobial resistance genes (ARGs) located on plasmids, transposons or integrons [10, 11]. NTS frequently infect sterile sites due to their invasive features. Most of these invasive NTS infections are bloodstream infections and also other focal infections [12]. In addition, infections caused by the AMR-NTS are associated with severer clinical outcomes and higher case fatality (14.5%) [13]. A recently emerged highly invasive multidrug resistant (MDR) *S.* Typhimurium strain has caused large epidemics in sub-Saharan Africa [14]. Similarly, a new variant of multidrug-resistant *S.* Typhimurium has been connected with invasive disease in immunocompromised patients [15, 16]. The new variant *Salmonella* Typhimurium in immunocompromised patients in Vietnam has been found resistant to fluoroquinolones, bleomycin, sulfonamides, trimethoprim, kanamycin, streptomycin, chloramphenicol, spectinomycin, florfenicol, hygromycin B, apramycin, beta-lactams, and rifampin [15].

Salmonella enterica infection is predominantly reported in immunosuppressed patients, such as those with cancer, HIV patients and in the aged population [17]. Additionally, certain serovars of *Salmonella* have been associated with other non-specific febrile illnesses such as bacteraemia, malignancy, hepatosplenomegaly, respiratory symptoms, which increased the risk of severe diseases and death from complications [18, 19]. It is widely established that cancer patients who undergo chemotherapy are more likely to get infections caused by *S. enterica*. Salmonellosis treatment in immunocompromised hosts requires a longer duration of treatment time compared with normal hosts [20].

In recent years, many studies have addressed the significance of salmonellosis in immunocompromised hosts, such as patients with acquired immunodeficiency syndrome or those undergoing in renal transplantation. However, limited attention has been given to its impact in cancer patients [21, 22]. AMR is a significant threat to human health and presents an even greater in immunocompromised cancer patients. The emergence of MDR is a major concern in *S. enterica* infections and leads to significant morbidity and mortality mainly in hospitalized cancer patients [23]. High rates of AMR are largely driven by frequent and irrational use of antibiotics and prolonged hospital stays. The use of antibiotics in treating bacterial infections in cancer patients has become clinically challenging due to their increasing resistance levels [24]. This study aimed to describe the serovar distribution, virulence gene profiles, AMR patterns and clonal relatedness of *Salmonella* spp. isolated from hospitalized cancer patients in Kolkata over an eight-year period (2016–2023).

Materials and methods

Study design

This prospective study was designed to characterize *Salmonella* isolates from different types of cancer patients who had undergone treatment in Tata Medical Center Kolkata from 2016 to 2023. All the confirmed isolates during this period were sent to ICMR-National Institute of Research in Bacterial Infections (ICMR-NIRBI) for serotyping confirmation and further characterization. Different samples were collected according to the patient's clinical presentation. The collected samples were sent to the Microbiology Department of Tata Medical Center, Kolkata, for the isolation and identification of the bacterial pathogens and antimicrobial susceptibility testing. Demographic and the clinical data of patients collected included age, sex, source and type of cancer.

Blood cultures were done using the BACT/ALERT system (BioMerieux, France) [19]. Bacterial identification was performed using Vitek-2 GN system (Biomerieux, France). Guidelines from CLSI (M-100, Clinical and Laboratory Standards Institute, USA) were used to interpret anti-microbial susceptibility test results [25]. Only the confirmed *Salmonella enterica* isolates were included in this study.

Serotyping of Salmonella spp

Each *Salmonella* spp. isolate was serotyped based on the White-Kauffmann-Le Minor scheme [26] using commercially available O and H antisera (S&A Reagents Lab Ltd., Bangkok, Thailand). All *Salmonella* isolates were preserved at −80 °C in sterile Trypticase soy broth with 50% glycerol for further studies.

Antibiotic susceptibility testing

Antimicrobial susceptibility testing was performed by the Kirby-Bauer disk diffusion method on Mueller-Hinton agar (Difco) and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [25] using the commercially available antibiotic discs (BD Co., Sparks, MD, USA) namely, cefotaxime (CTX, 30 µg), chloramphenicol (C, 30 µg), ofloxacin (OFX, 5 µg), doxycycline (D, 30 µg), gentamicin (GEN, 10 µg), ciprofloxacin (CIP, 5 µg), nalidixic acid (NA, 30 µg), levofloxacin (LVX, 5 µg ceftazidime (CAZ, 30 µg), azithromycin (AZM, 15 µg), ceftriaxone (CRO, 30 µg), trimethoprim-sulfamethoxazole (SXT, 1.25 and 23.75 µg), norfloxacin (NOR, 10 µg), erythromycin (E, 15 µg), tetracycline (TE, 30 µg), streptomycin (S, 10 µg), meropenem (MEM, 10 µg), and ampicillin (AM, 10 µg). *Escherichia coli* ATCC 25922 was used as the quality control strain in the assay.

Determination of virulence determinants

In this study, the presence of five SPIs was investigated by targeting the following genes: the *invA* gene for SPI-1 (helps in invasion), the *ssaQ* gene for SPI-2 (encodes type III secretion protein), the *mgtC* gene for SPI-3 (facilitates intramacrophage survival), the *spi4D* gene for SPI-4 (encodes type I secretion protein) and the *sopB* gene for SPI-5 (mediates inflammation and chloride secretion). In addition, the VP gene (*spvB-spvC*), plasmid encoded fimbriae (*pef*) gene and enterotoxin (*stn*) gene were also determined by end point PCR, using published primer sequences and PCR condition [27, 28]. The amplified products were analysed in a 2.5% (w/v) agarose gel in 1× Tris base, acetic acid and EDTA (TAE) buffer. Ethidium bromide (Sigma-Aldrich, USA) (0.5 µg/mL TAE) stained DNA amplicons were seen using a gel imaging system (BioRad, USA).

Pulsed-field gel electrophoresis (PFGE)

PFGE of *Xba*I digested genomic DNA of the study isolates was performed, using CHEF DRIII (Bio-Rad), following the PulseNet standard protocol [29]. *S.* Braenderup H9812 was used as a reference strain. In the clonal analysis, *S.* enteritidis, *S.* Kentucky, and *S.* Typhimurium isolates were investigated. Selection of these predominant serotypes was random, spanning all years of isolation. The PFGE profiles were analysed using BioNumerics software version 4.0 (Applied Maths, Sint-Martens-Latem, Belgium). The extent of homology was determined by Dice coefficient with 1.5% optimization and tolerance levels, and clustering of bands was done by Unweighted Pair Group Method with Arithmetic mean (UPGMA). The isolates with identical PFGE patterns (Dice coefficient of similarity of 100%) were described as genetically indistinguishable; isolates with PFGE patterns differing by three or less bands (Dice coefficient of similarity of > 80%) were designated as related and grouped under one cluster.

Statistical analysis

The association between *Salmonella enterica* serovars and types of cancer was evaluated using Fisher's exact test, with a p-value < 0.05 considered statistically significant; analyses were performed using R software (version 4.3.2).

Results

Demographic features and clinical characteristics

The demographic and clinical data of patients with salmonellosis enrolled in this study are shown in Table 1. Age group between 19 and 80 years ($n = 95/122$; 77.9%) showed higher isolation of *Salmonella* spp. than age group 6–18 years ($n = 14/122$; 11.5%) and children < 6 years ($n = 13/69$; 10.6%). Male patients ($n = 75/122$; 61.5%) were affected more than the female patients ($n = 47/69$; 38.5%). The most common source of the sample of *Salmonella* infection was blood ($n = 64/122$, 52.4%), followed by stool ($n = 45/69$, 36.9%), urine ($n = 7/122$, 5.7%), bile or body fluid ($n = 5/122$, 4.1%) and sputum ($n = 1/122$, 0.8%). *S*. Typhimurium, *S.* Enteritidis and *S*. Typhi were more prevalent in blood samples whereas *S*. Kentucky and *S.* Agona were isolated from stool samples.

Varying levels of Salmonella serotype prevalence

From July 2016 to December 2023, one hundred twenty-two *S. enterica* isolates were received by ICMR-NIRBI from Tata Medical Center, Kolkata. Each *S. enterica* was isolated from a single cancer patient who was admitted to the hospital for treatment i.e., a total of one hundred twenty-two patients were enrolled for this study. These isolates were sporadic cases that were associated with cancer patients admitted to the hospital for evaluation and treatment. *S. enterica* isolates were serologically classified into 18 different typable serovars (Table 1). Of the total of 122 isolates, the most common serovars were *S*. Typhimurium ($n = 35$; 28.7%), followed by *S*. Kentucky ($n = 27$; 22.1%), and *S*. Enteritidis ($n = 17$; 13.9%) (Table 1). The other serovars were *S.* Typhi ($n = 7$; 5.7%), *S*. Agona ($n = 7$; 5.7%), *S*. Hato ($n = 6$; 4.9%), *S.* Weltevreden ($n = 4$; 3.3%), *S.* Infantis, *S*. Paratyphi A, *S*. Virchow ($n = 3$, 2.4%, each), *S*. Bareilly, *S*. Stanley ($n = 2$, 1.6%,each), *S.* Aarhus, *S.* Derby, *S*. Haifa, *S*, Heidelberg, *S*. Senftenberg and *S.* Saintpaul, ($n = 1$, 0.8%, each).

The isolation rate of *Salmonella* spp. over the period of 8 years is shown in Table 2 The isolation rate remained relatively stable during the study period, but in 2023, the *Salmonella* spp. isolation rate reached its peak of 19.7% ($n = 24/122$,), followed by 2021 ($n = 21/122$, 17.2%), 2017 ($n = 20/122$, 16.4%), 2022 ($n = 19/122$, 15.6%) and 2018 ($n = 18/122$, 14.7%) while Lowest isolation rate was

Table 1 The distribution of identified *Salmonella* species in different clinical samples at Tata medical center, Kolkata from 2016 to 2023

***Salmonella* enterica serovar**	**No. of Isolates**	**Sex**		**Age (Years)**			**Source**				
		Male	**Female**	**< 6**	**6 to 18**	**19 to 80**	**Blood**	**Stool**	**Urine**	**Sputum**	**Pus cell, Bile**
Aarhus	1	1				1		1			
Agona	7	3	4	2		5	1	6			
Bareilly	2	2				2	2				
Derby	1		1			1		1			
Enteritidis	17	11	6		2	15	14	1			2
Haifa	1		1			1		1			
Hato	6	2	4	1		5	2	2	2		
Heidelberg	1	1				1	1				
Infantis	3	2	1		1	2		2	1		
Kentucky	27	18	9	3	1	23	9	14	2	1	1
Paratyphi A	3	2	1	1		2	1				2
Senftenberg	1		1			1		1			
Typhi	7	4	3		5	2	7				
Typhimurium	35	23	12	4	4	27	25	8	2		
Saintpaul	1		1	1				1			
Stanley	2	1	1	1		1	1	1			
Virchow	3	2	1			3		3			
Weltevreden	4	3	1		1	3	1	3			
Total	122	75	47	13	14	95	64	45	7	1	5

Table 2 The distribution of identified *Salmonella* species over the period of 8 years

***Salmonella enterica* Serovars**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**
Aarhus		1						
Agona			1	1		3		2
Bareilly				1			1	
Derby							1	
Enteritidis		4	1	1		6		5
Haifa								1
Hato			4					2
Heidelberg		1						
Infantis			1		1			1
Kentucky	1	6	5	1	2	2	5	5
Paratyphi A					1	1		1
Senftenberg							1	
Typhi			2	2			2	1
Typhimurium	3	4	3	1	5	7	7	5
Virchow		1	1				1	
Weltevreden		1				1	1	1
Saintpaul						1		
Stanley		2						
Total	4	20	18	7	9	21	19	24

observed in 2016 ($n=4/122$, 3.3%). *S.* Typhimurium and *S.* Kentucky were isolated throughout the study period with Maximal isolation during 2017, 2021, 2022 and 2023. Both the serovars were predominantly isolated from males than from female patients and adult (19–80 years) patients than children (Table 2).

Association between Salmonella serotypes and type of cancer

The association between isolation of *Salmonella* serovars and the type of diagnosed cancer is illustrated in Table 3. The highest number of *Salmonella* spp. isolated from acute lymphoblastic leukemia (ALL)/chronic myelogenous leukemia (CML) cancer patients ($n=30$, 24.6%). Patients with Hodgkin lymphoma/Non-Hodgkin lymphoma ($n=20$, 16.4%) showed the second highest isolation of *Salmonella* spp. followed by multiple myeloma ($n=12$, 9.8%), lung adenocarcinoma ($n=11$, 9.0%), prostate adenocarcinoma ($n=8$, 6.5%), endometrial carcinoma ($n=7$, 5.7%), stomach/colon adenocarcinoma ($n=6$, 4.9%), and gallbladder adenocarcinoma/cholangiocarcinoma ($n=5$, 4.1%).

Notably, the isolation rate of *S.* Typhimurium from ALL/CML patients was very high ($n=12/30$, 40%) compared to other serovars. In contrast, *S.* Kentucky and *S.* Enteritidis were mostly associated with multiple myeloma ($n=7/20$, 35%) and prostate adenocarcinoma ($n=7/8$, 87.5%) patients, respectively. Conversely, *S.* Hato was largely associated with lung adenocarcinoma (n- 4/11, 36.4%) patients. However, *S.* Typhimurium and *S.* Kentucky were equally isolated from stomach/colon adenocarcinoma patients ($n=3/6$, 50%, each). Although *S.* Typhimurium appeared more frequently in patients with hematologic malignancies, the association between cancer type and *S.* Typhimurium isolation was not statistically significant ($p=0.301$). In contrast, *S.* Kentucky showed a statistically significant association with hematologic malignancies ($p<0.001$), indicating a higher prevalence in these cancers compared to others. *S.* Enteritidis was also significantly more common in Hodgkin lymphoma and ALL/CML than in other cancer types ($p=0.004$). A borderline significant association was found for *S.* Typhi, which was more frequently isolated from patients with ALL/CML and multiple myeloma compared to others ($p=0.044$). We rarely encountered complications in NTS or TS. Sometimes bacteremia and sepsis rarely occur in ICU patients. Abscess has been rare in occurrence of subcutaneous intramuscular abscess and vertebral osteomyelitis.

Description of AMR among Salmonella isolates

The percentage of AMR in *Salmonella* spp. isolates is shown in Fig. 1. Overall, most of the *Salmonella* spp. displayed resistance to nalidixic acid (62.9%), erythromycin (62.9%), tetracycline (33.9%), ofloxacin (25.8%), ciprofloxacin (24.2%), norfloxacin (24.2%), and ampicillin (24.2%), whereas all the isolates were susceptible to meropenem (100%) followed by ceftazidime (95.2%), trimethoprim-sulfamethoxazole (93.6%), cefotaxime (93.6%), gentamicin (90.3%), ceftriaxone (87.1%) and azithromycin (87.1%). *S.* Kentucky was mostly resistant to erythromycin (100%), doxycycline (91.7%). tetracycline (91.7%), ampicillin (83.3%), ofloxacin (83.3%), ciprofloxacin, norfloxacin and nalidixic acid (75%, each)

Table 3 The association between identified *Salmonella* serovars with diagnosed cancer patients

Types of Cancer or Infection	Total No of Salmonella enterica Isolated	*Salmonella enterica* Serovars																	
		Typhimurium	Kentucky	Enteritidis	Aarhus	Agona	Bareilly	Derby	Haifa	Hato	Heidelberg	Infantis	Paratyphi A	Senftenberg	Typhi	Virchow	Weltevreden	Saintpaul	Stanley
Acute Lymphoblastic Leukemia (ALL)/ Chronic myelogenous leukemia (CML)	30	12	3	3	1	1			1	2		1			4		1		1
Hodgkin Lymphoma/Non-Hodgkin Lymphoma	20	6	7	4		1											1		1
Lung adenocarcinoma	11	2		2			1			4	1					1			
Prostate adenoocarcinoma	8			7									1						
Uterus/Endometrium carcinoma	7	2	1	1		1						1					1		
Relapsed Mantle cell lymphoma/ Stem cell	4		2												1	1			
Stomack/ Colon Adenocarcinoma	6	3	3																
Gallblader adenocarcinoma/ Cholangiocarcinoma	5	1	1			1	1						1						
Multiple myeloma	12	4	6									1			1				
Oral Cavity Ca	1	1																	
Multifocal residual sarcoma	1														1				
Brain Cerebellum Desmoplastic medulloblastoma	1					1													
Carcinoid tumor	1	1																	

Table 3 (continued)

Types of Cancer or Infection	Total No of Salmonella enterica Isolated	*Salmonella enterica* Serovars																	
		Typhimurium	Kentucky	Enteritidis	Aarhus	Agona	Bareilly	Derby	Haifa	Hato	Heidelberg	Infantis	Paratyphi A	Senftenberg	Typhi	Virchow	Weltevreden	Saintpaul	Stanley
Neuroblastoma	1							1											
Ewing Sarcoma Spine	1	1																	
Breast lump	1		1																
Paratyphodial Fever	1												1						
Hypopharyngeal cancer	1	1																	
Ovarian cancer	4		1											1		1		1	
Kidney Adenocarcinoma	2	1	1																
Liver Adenocarcinoma	1		1																
Pancreas Adenocarcinoma	3					2											1		
Total	122	35	27	17	1	7	2	1	1	6	1	3	3	1	7	3	4	1	2

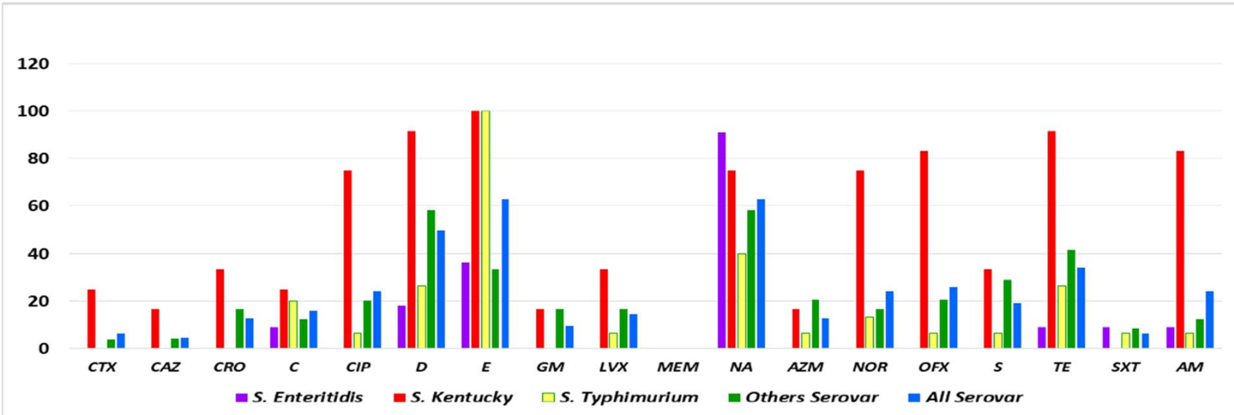

Fig. 1 The percentage of antimicrobial resistance (AMR) profile in *Salmonella* spp. identified from cancer patients

while, *S*. Typhimurium displayed resistant to erythromycin (100%), nalidixic acid (40%), tetracycline (26.7%) and doxycycline (26.7%). *S*. Enteritidis showed resistance to nalidixic acid (90.9%), and erythromycin (36.4%). There are eight different resistance profiles found in *S*. Kentucky followed by six in *S*. Typhimurium and five in *S*. Enteritidis. None of the isolates of *S*. Typhimurium and *S*. Enteritidis showed resistance to third generation cephalosporins. The Minimum Inhibitory Concentration (MIC) against azithromycin in the *S*. Typhi isolates were normally distributed and ranged between 0.75 µg/mL and 4 µg/mL (Table S1). Overall, the resistance profiles of other *Salmonella* spp. isolates displayed a similar resistance pattern.

Identification of virulence genes

The prevalence and distribution of different virulence genes in *Salmonella* spp. were shown in Table 4. The majority of the isolates harbored at least one gene associated with virulence. The most dominant virulence genes detected in this study are *orgA*, (81.2%) followed by *hilA* (76.4%), *ssaQ* (73.9%), *stn* (69.2%), *misL* (60.2%) and *invE/A* (57.2%). The distribution of virulence genes showed that 87.5% of *S.* Kentucky carried *hilA*, 81.2% carried *misL*, and *stn*, 75% carried *invE/A* and *orgA*, 68.7% carried *ssaQ*, *spi4D*, *sopB*, and 43.7% of them carried *ttrc* gene. In *S*. Typhimurium, 94.4% carried *ssaQ*, 83.3% carried *orgA*, 77.7 s carried *pipA* and *hilA*, 72.2% carried *sopB* and *stn* and 61.1% carried *invE/A* gene. About 86% of *S*. Enteritidis carried *org*, 78.5% carried *hilA*, 71,4% carried *stn* and 57.1% carried *ssaQ*, *misL*, *sopB*, and *spvC* genes. However, all the *S. enterica* isolates were negative for *spi4R* gene.

Clonal analysis of predominant serotypes

The clonal relatedness of *S*. Typhimurium, *S*. Kentucky, and *S*. Enteritidis isolates was investigated using PFGE. This technique was applied to a random selection of isolates spanning all years of isolation to assess their genetic relatedness. Analysis of the PFGE patterns of all three serovars revealed three clusters (A to C) with ~ 50% similarity coefficient (Fig. 2A, S. Typhimurium; 2B, *S*. Kentucky and 2C, *S*. Enteritidis). PFGE of 12 *S*. Typhimurium representative isolates, cluster A showed a similarity coefficient of 85% and cluster B showed an 80% homology between the isolates). In *S*. Kentucky isolates, Cluster A and B had 80% similarity, whereas Cluster C was represented by 2 isolates with an overall similarity coefficient of ~ 45%. Nine *S*. Enteritidis strains although found to be genetically unrelated, yet few closely related strains (cluster A and cluster B) showed ~ 70% similarity co-efficient.

Discussion

Cancer has become a global public health issue in recent years, and millions of people are dying due to cancer each year worldwide [30]. Biological mechanisms, including the presence of pathogenic bacteria like *Helicobacter pylori*, as well as physical and chemical agents have been implicated in the onset and progression of gastric cancer [31]. Infection remains an important cause of morbidity and mortality among patients with cancer. Infections in cancer patients cause changes in the treatment plan, extended hospitalization, increased cost of health care, and reduced survival [32]. Infection-related complications can be life-threatening if not detected and treated early [33]. Important infections in cancer patients like bloodstream infections, acute gastrointestinal infections, urinary tract infections and pneumonia are the major contributors to mortality [34]. *S. enterica* comprises several serovars, including *S.* Typhi and *S.* Paratyphi and *S.* Typhimurium. The most common clinical expression of *Salmonella* infection is acute gastroenteritis [2]. However, *S. enterica* infection can present with extra-intestinal manifestations, including fever and bacteraemia without enteric fever in some cases, as well as focal

Table 4 The prevalence and distribution of different virulence genes in *Salmonella* spp

Salmonella enterica serovar	*Salmonella* pathogenicity islands (SPIs)										Plasmid encoded fimbriae	Hyper invasive locus	*Salmonella* outer protein	*Salmonella* Enterotoxin	Virulence plasmid
	SPI 1		SPI 2		SPI 3		SPI 4		SPI 5						
	invE/A	**orgA**	**ttrc**	**ssaQ**	**mgtC**	**misL**	**spi4R**	**spi4D**	**sopB**	**pipA**	**pefA**	**hilA**	**SopB**	**stn**	**spvC**
Enteritidis	64.2	85.7	35.7	57.1	-	57.1	-	50	57.1	35.7	-	78.5	35.7	71.4	57.1
Kentucky	75	75	43.7	68.7	12.5	81.5	-	68.75	68.75	56.25	-	87.5	31.2	81.2	12.5
Typhimurium	61.1	83.3	27.7	94.4	16.6	50	-	44.4	33.3	77.7	44.4	77.7	72.2	72.2	50
Other serovar	28.5	80.9	61.9	75.4	28.5	52.3	-	52.3	9.5	52.3	23.8	61.9	66.6	52.3	9.5
Total	57.2	81.2	42.2	73.9	14.4	60.2	-	53.8	42.1	43.7	17	76.4	51.4	69.2	32.2

infections including septic arthritis, osteomyelitis, vascular infection, endocarditis, urinary tract infection and splenic abscess [18], especially in the immunocompromised hosts. In this study, we showed the presence of *S. enterica* infection and its virulence potential and patterns of antibiotic resistance in cancer patients.

Patients with different categories of cancer have an increased risk of acquiring *S. enterica* infections because of the disruption of the mucosal barrier caused by cancer and/or cancer therapy, immunodeficiency caused by cancer and the use of corticosteroids or cytotoxic chemotherapy [20, 21]. Our data showed that *S. enterica* causes severe infections in cancer patients, particularly in those with leukemia and Hodgkin lymphoma or non-Hodgkin lymphoma [35]. Leukemia is the sixth most prevalent Malignancy, Making up around 6.8% of all malignancies in India [36]. Among the patients found to have *Salmonella* infection, 26% had leukemia. Gokturk et al. reported that non-hodgkin lymphoma might increase the risk of *Salmonella* infection [37]. Among the patients who had *Salmonella* infection, 16.4% had lymphoma. Among patients with salmonellosis 9.8% and 9% had multiple myeloma and lung cancer respectively. These patients generally had mucosal barrier disruption and other anatomic or physiologic abnormalities that facilitate infection [38, 39].

We identified a wide distribution of *S. enterica* serovars among cancer patients. The most common NTS include *S.* Typhimurium (28.7%), *S.* Kentucky (22.1%), *S.* Enteritidis (13.9%) and *S.* Agona (5.7%). Previous studies in the USA on NTS in cancer patients have reported similar trends in dominance of *S.* Typhimurium and *S.* Enteritidis serovars [20]. It was shown that NTS is a cause of severe infections in cancer patients, particularly in those with hematologic malignancies and gastrointestinal cancers [20]. Infection caused by *S.* Typhi is very common in Southeast Asia, especially in the Indian subcontinent [1]. Studies featuring the incidence of *Salmonella* serotypes among cancer patients are very few. Some of the recent studies indicated association of *S.* Typhimurium, *S.* Typhi with gallbladder cancer [40, 41], *S.* Typhi and *S.* Paratyphi A with colon cancer [42], *S.* Worthington with chronic myeloid leukemia [43].

The clinical complications in TS and NTS infections may not vary in cancer patients [20, 44]. The average duration of hospitalization for Typhoid patients in our center is between 10 and 14 days and for those with NTS infections between 5 and 7 days. In most cases of NTS infection, the clinical presentation was gastroenteritis with diarrhea with stool consistency varying between liquid and semi-solid. In TS infection, fever remains commonest presentation. The frequent problems and complications of NTS and TS infection in cancer patients include: admission to the hospital, delay in chemotherapy

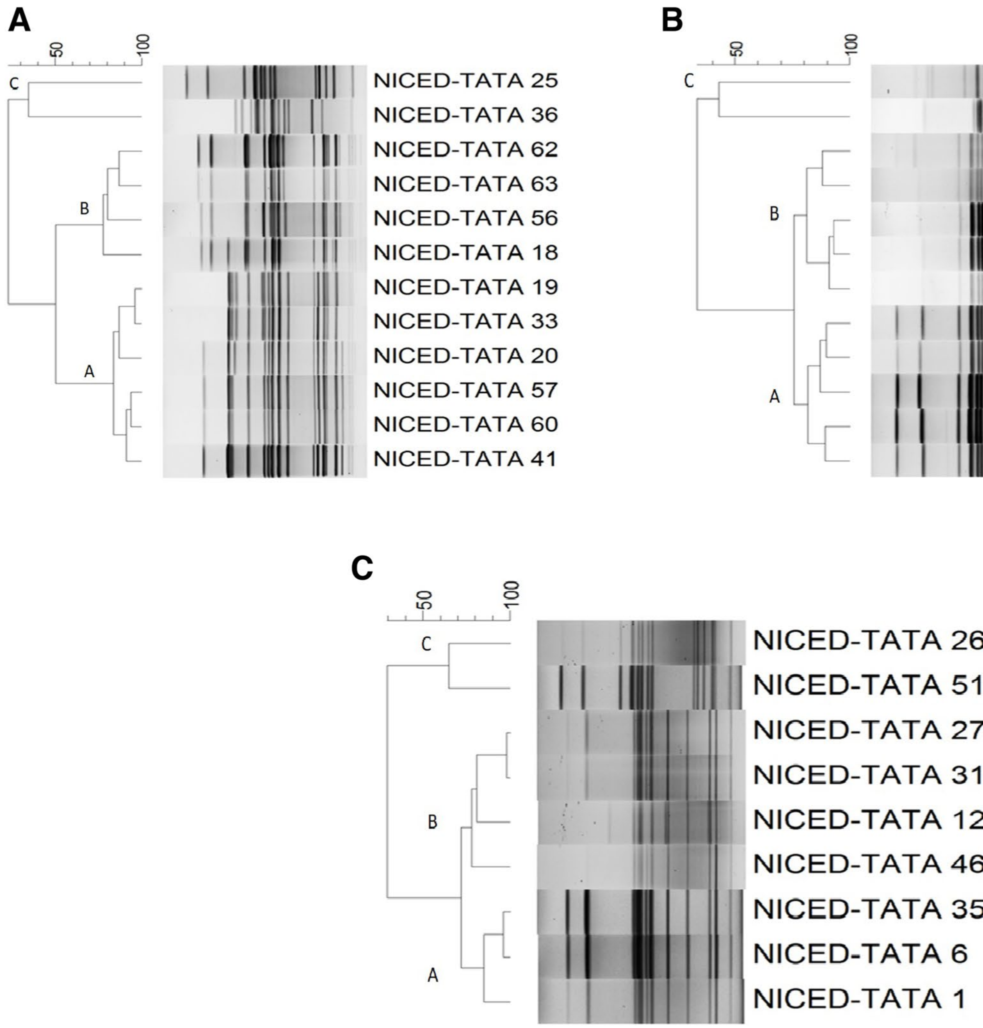

Fig. 2 Pulsed-field gel electrophoresis analysis of *Xba*1-digested genomic DNA of *Salmonella enterica* isolated from diagnosed cancer patients in Kolkata, India. Fig. 2**A**:*S.* Typhimurium; Fig. 2**B**: *S.* Kentucky and Fig. 2**C**: *S.* Enteritidis

or other cancer-specific treatments. NTS infections are self-limited and specific antibiotics might not be necessary. Some of these patients responded to oral and intravenous rehydration therapy. In case of NTS-associated bacteraemia, the NTS infections are treated like typhoid patients.

TS infections on the other hand presented with fever of unknown origin (FUO). These patients are always treated with intravenous and oral antibiotics. Generally, the first 7–10 days they were treated with IV antibiotics (ceftriaxone 2 gm IV, cefixime 200 mg oral Q12H; Q12H. meropenem- 1 gm IV Q8H) along with oral azithromycin (1 gm on day 1; then 500 mg Q24H for at least 7 days). The total duration of antimicrobial therapy was 14 days, extending to 3–4 weeks in case of abscesses.

MDR refers to MDR *Salmonella* isolates, which are resistant to at least three different classes of antibiotics. The rise of MDR *S. enterica* is becoming a significant issue for public health and is commonly encountered among immunocompromised, excess bloodstream infections and hospitalizations patients [45]. In our study, we explored the AMR patterns of different serovars of *Salmonella* identified from cancer patients. Chemotherapy was the most common mode of treatment for cancer patients enrolled in this study. Most of the *Salmonella* isolates were resistant to nalidixic acid (62.9%), erythromycin (62.9%), tetracycline (33.9%), ofloxacin (25.8%), ciprofloxacin, norfloxacin and ampicillin (24.2%), which is similar to a previous study [46].

At our center, antibiotic resistance patterns in typhoidal and NTS infections revealed azithromycin (4–5%), quinolone resistance (75%), and third generation cephalosporins (8–9%). Due to the high prevalence of quinolone resistance (notably to ciprofloxacin and levofloxacin), these drugs are no longer recommended in our centre for the empirical therapy of *Salmonella* infections and are reserved solely for directed treatment when in vitro susceptibility is confirmed. Currently, the preferred therapeutic approach consists of combination therapy with azithromycin and a third-generation cephalosporin (intravenous ceftriaxone or oral cefixime). Treatment failures with this regimen have been uncommon. However, in cases of persistent fever or clinical non-response, ceftriaxone is substituted with meropenem for 5–7 days. Such escalation has been necessitated by the detection of ESBL producing *Salmonella* isolates.

All *S*. Kentucky isolates showed MDR to several tested antimicrobials tested. MDR seems more common in this serovar and has been reported from various countries [47, 48]. Fluoroquinolone and tetracycline resistance were exclusively observed in *S*. Kentucky serovar. Intermediate resistance signifies the pathogen isn't fully resistant but also not fully susceptible to the antibiotic, which can result in suboptimal response to therapy. Infections like salmonellosis, especially invasive or severe cases, can be difficult to treat if resistance levels are rising. Encouragingly, most of the TS and NTS remained susceptible to ceftriaxone, cefixime, and azithromycin, which therefore continue to serve as effective treatment options. No consistent correlation was identified between AMR pattern and specific clonal genotypes of *S*. Typhimurium, *S*. Kentucky and *S*. Enteritidis isolates. PFGE subtyping of these predominant serotypes demonstrated high genetic relatedness, with similarity coefficients exceeding 70–80%. This observation aligns with previous global studies, which have also reported close clonal resemblance among isolates of these major serotypes [10, 49].

In India, *S.* Worthington isolated from a chronic myeloid leukemia patient was reported to be resistant to ampicillin, gentamicin, cefotaxime, chloramphenicol and tetracycline [43]. In this study, PFGE analysis showed inter-serotype genetic similarity among *S*. Enteritidis, *S.* Kentucky and *S*. Typhimurium. Despite this genetic relatedness, clear differences in the AMR profiles were observed. Consistent with earlier reports, *S*. Enteritidis demonstrated considerable clonal diversity, but uniformly exhibits higher resistance to nalidixic acid [50, 51], while remaining largely susceptible to most other antimicrobial agents [52]. In contrast, *S.* Kentucky displayed high clonal similarity in PFGE and exhibited MDR, especially to fluroquinolones and cephalosporins, an observation corroborated by previous studies [53, 54]. Similarly, *S*. Typhimurium isolates in this study exhibited high genetic similarity, in line with earlier findings [55]. However, other reports also documented the MDR pattern in this serotype predominantly to tetracycline, streptomycin, ampicillin, nalidixic acid, chloramphenicol [56, 57].

This study demonstrated that *S*. Typhimurium, *S*. Kentucky and *S*. Enteritidis were the predominant serovars responsible for infections in cancer patients; although other serovars also contributed to disease burden. The observed spectrum of antimicrobial resistance, ranging from low to high levels across isolates, together with the diverse virulence gene profiles, underscores a significant clinical concern. These findings highlight emerging challenges for healthcare providers and clinicians in both therapeutic management and infection control. To mitigate morbidity and prevent further dissemination, comprehensive clinical and epidemiological investigations are urgently warranted, with particular emphasis on cancer patients who remain especially vulnerable to *S. enterica* infections.

Different *Salmonella* serotypes exhibit varying distributions of virulence genes, meaning there is no single set of virulence genes common to all serotypes. This variation contributes to the diversity of *Salmonella* pathogenesis, with some serotypes causing more severe disease than others [58, 59]. In the present study, the predominant virulence genes detected in this study in all the serotypes include *invE/A* (invasion of host epithelial cells), *orgA* (outer ring of the invasion gene cluster A), *hilA* (key transcriptional regulator of host cell invasion) and *stn* (encodes a heat-stable enterotoxin). Notably, none of the serotypes harboured the *spi4R* gene. Similarly, *pefA* (plasmid-encoded fimbriae) was absent in *S*. Enteritidis and *S*. Kentucky. In *S.* Enteritidis, *ssaQ* (secretion system apparatus Q), *pipA* (effector gene of *Salmonella* T3SS) genes are relatively less compared to the other serotypes. *mgtC* (magnesium transport A, for survival in macrophages), *sepB* (*Salmonella* extracellular protein B invasion) and *spvC* (*Salmonella* plasmid virulence C responsible for systemic infection) genes are detected in less proportion in *S.* Kentucky. Similarly, in *S.* Typhimurium, a reduced prevalence of *ttrC* (tetrathionate reductase-C), *mgtC*, *misL* (membrane insertion and secretion), *spi4D* (*Salmonella* Pathogenicity Island 4, region invade host cells, survive within the host), and *sopB* (*Salmonella* outer protein B) was observed. This serotype-specific distribution of virulence genes highlights the genetic heterogeneity of *Salmonella* and provides a basis for understanding differences in clinical severity, host adaptation, and pathogenic mechanisms.

Conclusion

Salmonella infection in cancer patients presents a serious and potentially life-threatening complication, due to their immunocompromised state resulting from the malignancy itself or its therapeutic interventions. Key predisposing factors include neutropenia, mucosal barrier damage, immunosuppression and prolonged hospital exposure. Timely diagnosis coupled with appropriate antimicrobial therapy remains central to effective management of salmonellosis in this vulnerable group. It is therefore imperative that oncologists, microbiologists, infection control practitioners, and public health officials need to be aware of *Salmonella* infections as a significant concern in cancer patients due to the increased risk of complications and severe illness. Strengthening targeted health education and ensuring evidence-based clinical management are crucial for preventing and managing these infections in this vulnerable population. In continuation, our current focus is on whole-genome sequencing of predominant *Salmonella enterica* serotypes isolated from cancer patients. This genomic approach will provide comprehensive insights into antimicrobial resistance determinants, virulence factors, core genome MLST, and the pangenome architecture of the pathogen, thereby contributing to improved strategies for surveillance, prevention, and therapeutic intervention.

Abbreviations

NTS	Non-typhoidal *Salmonella*
SPI	*Salmonella* pathogenicity island
PFGE	Pulsed-field gel electrophoresis
CML	Chronic myelogenous leukemia
ALL	Acute lymphoblastic leukemia
AMR	Antimicrobial resistant
MDR	Multidrug resistant
WHO	World Health Organization
ARGs	Antimicrobial resistance encoding genes
XLD	Xylose lysine deoxycholate
HE	Hektoen enteric
CLSI	Clinical and Laboratory Standards Institute
HilA	Hyper invasive locus
Stn	*Salmonella* enterotoxin
SopB	*Salmonella* outer protein
SpvC	Virulence plasmid
PefA	Plasmid encoded fimbriae

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Goutam Chowdhury, Sanjay Bhattacharya, Thandavarayan Ramamurthy, Asish K. Mukhopadhyay conceived and designed the study; Goutam Chowdhury, Gaurav Goel, Soumyadip Chatterji, Kei Kitahara, Ayumu Ohno, Melissa Glenda Lewis collected the data, performed the experiment and analysis; Goutam Chowdhury wrote the first draft of the manuscript; Sanjay Bhattacharya, Shin-ichi Miyoshi, Thandavarayan Ramamurthy, Asish K. Mukhopadhyay supervise the study and manuscript preparation. The authors read and approved the final manuscript.

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Data availability
All data and material for this study has been provided in the article.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and relevant guidelines. Informed consent was obtained from each adult patient or the parent/guardian of the child patient enrolled in this study. The study was reviewed and approved by the " Institutional Ethics Committee (IEC)" at the ICMR - National Institute for Research in Bacterial Infections, Kolkata, India (registration number: A-1/2021-IEC) and the Institutional Review Board of Tata Medical Center, Kolkata (IRB reference number > EC/GOVT/04/13).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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