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ORIGINAL ARTICLE

Assessment of Liver and Renal Function Tests among patients with typhoid fever in Motta General Hospital, Northwest Ethiopia*: A* Comparative Cross-Sectional Study

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ABSTRACT

Background: Typhoid fever remains an important cause of morbidity and mortality in developing countries with poor hygienic conditions and limited access to safe drinking water. It primarily has an impact on the liver and the kidney organs which causes liver and renal function test to be affected. And now, this study was to evaluate liver and renal function tests in typhoid fever patients at Motta General Hospital Northwest Ethiopia, May to December 2023.

Method: Hospital-based comparative cross-sectional study was conducted in Motta General Hospital on 90 typhoid fever patients and 90 control groups were selected by convenience sampling technique. Data was analyzed by SPSS version 26 after collecting all clinical and laboratory data. Statistical significance was defined as a p-value < 0.05.

Result: The average age of the typhoid fever cases was 32.23± 13.48 years, and control subject was 32.62±7.708. Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin and creatinine values were significantly higher among typhoid fever patients than control groups.

Conclusion: Typhoid fever appeared to significantly affect liver function tests (ALT and AST, ALP, TB and DB) and renal function tests (creatinine) compared to controls. Abnormal liver and renal functions tests in typhoid fever is more common with patients presenting in 2nd and 3rd week of illness.

Keywords: Typhoid fever, Liver function tests, Renal function tests

INTRODUCTION

Typhoid fever is a systemic infection and continues to be the key cause of morbidity and mortality in developing countries with poor hygienic practices and limited access to safe drinking water[1]. Typhoid fever is thought to affect 11–20 million people and approximately 128,000–161,000 deaths annually worldwide[2]. Developing countries contributed around 12.5 million of the global cases[3,4]. The *salmonella* bacteria are transmitted through contaminated food and water. The bacteria invade the walls of the intestines and cause bacteremia through the profusion of bacteriaina person's bloodstream, which invades the liver, kidney and other Organs[5]. In addition to the systemic infection, the liver organ can expose the bacteria directly via the gut-liver axis[6].

In invasive *salmonella* infection, pattern recognition receptors (PRRs) recognize pathogen- associated-molecular-patterns (PAMPs) and danger-associated molecular patterns (DAMPs) stimulate the innate immune system which cause activation of macrophages and produce inflammatory chemicals like interferon-gamma (IFN)-γ, tumor necrosis factor (TNF)-α, IL-1β, and Interleukin (IL)-6. IFN-γ regulates the level of macrophage activation, which is the primary mechanism by which persistent infection is controlled[7,8].

Kupffer cells are liver macrophages that phagocytose S. Typhi which then evades immune surveillance. To antagonize pathogenic invaders, macrophage cells secrete reactive oxygen species (ROS such as hydrogen peroxides, superoxides anion, and hydroxyl radicals) and reactive nitrogen species (RNS including nitric oxide and peroxynitrite)[9,10] but salmonella bacteria express superoxide dismutase which encodes an enzyme necessary for the detoxification of superoxide anion and catalyzes the detoxification of nitric oxide and is required to maintain a chronic Salmonella infection[9,10].

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Most of the virulence genes of Salmonella species are located on Salmonella pathogenicity islands (SPI) The Salmonella pathogenicity island-1 (SPI-1) locus encodes a type III protein secretion system (TTSS) that injects effector proteins necessary for liver penetration. The SPI-1 effect or Sip B triggers caspase-1 activation in macrophages, followed by a rapid cell death with characteristics of both apoptosis and necrosis. The second region of virulence-associated specific DNA necessary for survival in the liver during infection and replication in macrophage cells is SPI-2, which encodes specialized TTSS. The SPI-2 effect or proteins, for example, bestow the capacity of Salmonella strains to multiply in macrophages resultant in delocalized infection[11-13]. In this regards uncontrolled activation of the innate as well as adaptive immune response can lead to harmful inflammation and tissue injury in the liver organ. When that occurs, transaminase and membranous alkaline phosphatase, enzymes of the liver, leak out and enter the circulation and increase the enzyme levels.

Twenty to forty percent of patients excreted Salmonella in the urine, usually during these condor third week of the disease. Toxic nephrosis, the development of micro-abscesses, or the creation of metastaticfoci in the kidney is due to the passage of salmonella bacteria through the intact kidney in typhoid fever, which causes glomerulonephritis. Glomerulonephritis leads to abnormal function of the kidney in the elimination of waste products including creatinine and urea which causes an increase in those chemicals[14,15]. Even though typhoid fever is a top health challenge there is no published study conducted in Ethiopia, particularly in the study area.

This study aims to assess the level of liver and renal function tests among patients with typhoid fever.

METHOD AND MATERIAL

Study setting, design, and period: The study was conducted at Motta General Hospital. Motta is at own in northwest Ethiopia found in the east Gojam Zone of the Amhara Region. Around1.2

million people in the surrounding area were served by the hospital. An institutional-based comparative cross-sectional study was conducted from May to December 2023 among 90 typhoid fever and 90 control subjects.

Study Population and Sampling Method: The study subjects of this study were typhoid fever patients and apparently health staff members and apparent students of Motta General Hospital selected with a convenient sampling technique.

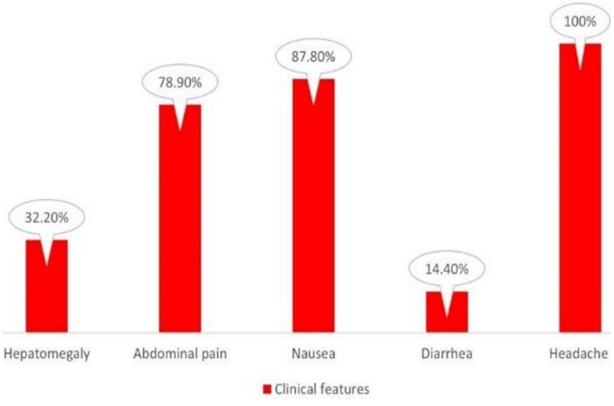
Eligibility criteria: Inclusion criteria were typhoid fever patients who attended Motta General Hospital during the study period and who were willing to participate in the study for the case group, all apparently healthy staff members and apparent students of Motta General Hospital, who were matched with cases in age and sex and volunteered to participate in the study for the control group. The exclusion criteria were participants who had chronic liver, heart, and renal diseases, positive malaria tests, and pregnant women for both case and control groups.

Study Variables: Liver function tests (AST, ALT, ALP, DB, and TB) and renal function tests (creatinine and urea) were dependent variables, socio-demographic characteristics, and clinical features were an independent variable of this study.

Data collection and measurement: A semi-structured translated and pretested questionnaire was used to collect socio-demographic and clinical data. After the collection of 3-5ml of blood sample, the serum was analysed for renal function (creatinine and urea) and liver function (ALT, AST, ALP, DB, and TB) by Cobas c311 automated chemistry analyzer.

Data quality assurance: The questionnaires were translated into the local language Amharic to make it easily understood by the participants and ten percent of participants were pre-tested before the real data collection. The blood sample was also collected in aseptic techniques to avoid hemolysis and other interferences. Before the participant sample run, both pathological and normal control samples were tested and the sample was analysed after both control values were accepted. Finally, all information was recorded in the unique code of each subject and check its completeness and consistency.

Figure 1: Clinical features of typhoid fever patients in Motta General Hospital, Northwest Ethiopia, May to December 2023.



Data analysis: After collection of all clinical and laboratory data the data was entered in SPSS version 26 for analysis. As the data has a skewed distribution use anon-parametric test (Mann-Whitney U test and the Kruskal-Wals test). A p-value < 0.05 was taken as statistically significant.

Typhoid fever (case group): a febrile illness patient who has positive for rapid salmonella stool antigen test and an antibody titer of ≥ 1:80.

Apparently healthy (control group): An individual without any symptoms or signs of illness, with a negative rapid stool antigen test result for salmonella and non-reactive for widal test.

Ethical consideration: Ethical clearance was obtained from the research and ethics committee of Addis Ababa University Medical Laboratory Science Department (Reference number. MLS/047/23). Written informed consent and assent were obtained from the study participants before the commencement of data and specimen collection after the purpose of the study was explained. Confidentiality of participants' information was maintained by employing a special code.

RESULTS

Socio-demographic Characteristics of study participants: This study includes 90 typhoid fever subjects (53 males and 37 females) and 90 control groups (46 males and 44 females). The mean age±SD of typhoid fever patients and controls was33.10±12.11 years and 32.62±7.708 years respectively. 58.9% of typhoid fever cases and11.1% of the control group were live in rural areas. About 65.6% of typhoid fever cases and 76.6% of control groups were married. About 27.8% of typhoid fever cases were a farmer and 86.7% of control groups were government employees. 35.6% of typhoid fever cases had no formal education and 92.2% of controls were diploma and above. Almost 97% of typhoid fever cases and 96% of the healthy group were normal BMI (Table 1).

Table 1: Socio-demographic characteristics of typhoid fever patients and controls in Motta General Hospital, Northwest Ethiopia, May to December 2023

Socio-demographic character		Case(n=90)	Control(n=90)
Sex	Male	53(58.9%)	46(51.1%)
	Female	37(41.1%)	44(48.9%)
Age in year	<25	29(32.2%)	20(22.2%)
	25-34	16(17.8%)	35(38.9%)
	≥ 35	45(50.0%)	35(38.9%)
Mean ±SD		33.10 ± 12.11	32.62 ± 7.708
Residence	Urban	37(41.1%)	80(88.9%)
	Rural	53(58.9%)	10(11.1%)
Occupation	Government Employee	6(6.7%)	78(86.7%)
	Merchant	11(12.2%)	0
	Farmer	25(27.8%)	0
	Housewife	19(21.1%)	0
	Student	29(32.2%)	12(13.3%)
Educational status	No formal education	32(35.6%)	0
	Primary	30(33.3%)	3(3.3%)
	Secondary/preparatory	13(14.4%)	4(4.4)
	Diploma and above	15(16.6%)	83(92.2%)
Family member	<5	84(93.3%)	83(92.2%)
	≥5	6(6.7%)	7(7.8%)
BMI	<18	3(3.3%)	0
	18-25	87(96.7%)	86(95.6%)
	>25		4(4.4%)
Mean± SD		20.33±1.37	21.93±1.74

SD=Standard deviation, BMI=Body mass index

Clinical features of typhoid fever patients

The clinical signs and symptoms in typhoid fever cases were: headache (100%), abdominal pain (78.9%), diarrhoea (14.4%), nausea (87.8%), and hepatomegaly (32.2%) (Figure 1).

Comparison of Liver and Renal Parameters among typhoid fever and control group

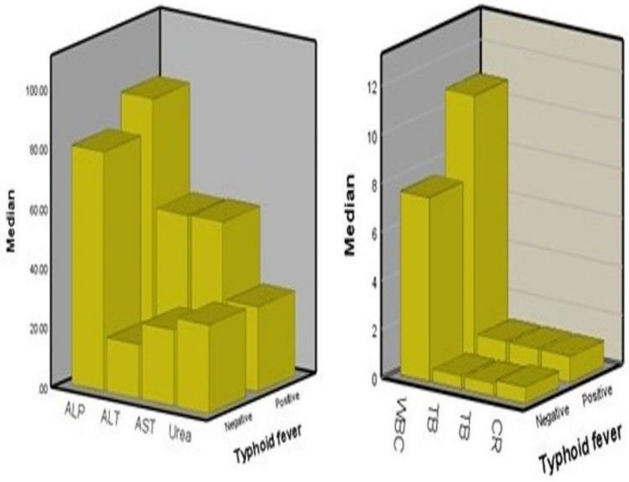
Liver enzymes, AST, ALT, and ALP were significantly higher in typhoid fever cases than in control groups with median±IQR (54.35±78.33 versus 25.45±11.23, P<0.001), (54.05±78.33 versus 18.10 ±12.27, p<0.001) and (90.50±74.25 versus 80.00 ±54, p<0.001) respectively. Similarly, levels of TB and DB were significantly higher among typhoid fever patients compared to control groups (0.80±1.2 versus 0.504±0.302, p<0.001), (0.174±0.76 versus 0.113 ± 0.097, p=0.002) respectively. Renal function test creatinine was significantly higher in typhoid fever than in control groups with median±IQR1.07±0.69 versus 0.68±0.19, p<0.001 (Table2, Figure 2).

Table 2: Comparison of liver and renal function tests among typhoid fever and control study participants in Motta General Hospital, Northwest Ethiopia, May to December 2023.

Parameter	Case group (n=90)	Control group (n=90)	P-value
	Median ±IQR	Median ±IQR	
ALT(U/L)	54.05±78.33	18.10 ±12.27	<0.001
AST(U/L)	54.35±78.33	25.45 ±11.23	<0.001
ALP(U/L)	90.50±74.25	80.00 ±54	<0.001
AST: ALT	1.29±0.38	1.4±0.46	0.005
TB (mg/dl)	0.80±1.2	0.504 ±0.302	<0.001
DB (mg/dl)	0.174±0.76	0.113 ±0.097	0.002
CRE (mg/dl)	1.07±0.69	0.68 ±0.19	<0.001
Urea (mg/dl)	29.20±11.43	29.60 ±13.05	0.171
WBC (X10^3/µL)	11.73±4.62	7.18 ±3.69	<0.001

IQR-Interquartile range, n-number of participants, ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, ALP-Alkaline phosphatase, TB- Total bilirubin, DB-Direct bilirubin, WBC-White blood cell, and BMI-Body mass index.
Mann-Whitney U test was used for comparison

Figure 2: 3-D bar graph representation of liver and renal function tests comparison among typhoid fever and control groups in Motta General Hospital, Northwest Ethiopia, May to December 2023.



Durationofillnessintyphoidfeverpatientsandliverandrenalfunctiontest results

Duration of illness had effects on liver and renal function tests of typhoid fever patients. ALT, ALP, TB, and Creatinine levels of typhoid fever study subjects of greater than or equal to three- week duration were significantly higher than study subjects exposed for less than or equal to one week and two weeks (Table 3, Figure 3).

Table 3: The association of duration of illness on Liver and Renal function tests of typhoid fever patients in Motta General Hospital, Northwest Ethiopia, May to December 2023.

Parameters	Duration of illness		
	≤ one week (n=68) (Median±IQR)	Two weeks (n=20) (Median±IQR)	≥Three weeks (n=2) (Median±IQR)
ALT(IU/L)	42.6±51.05[a,b]	89.8±87.8	130.35
AST (IU/L)	50.7±61.25[a]	103.05±113.62	121.2
ALP(IU/L)	88±67.75[a,b]	158.5±147.25	203
TB (mg/dl)	0.71±0.898[a,b]	1.63±1.93	2.41
DB (mg/dl)	0.15±0.27[a]	0.79±1.35	1.25
Creatinine (mg/dl)	0.97±0.69[a,b]	1.19±0.44	1.38
Urea (mg/dl)	28.55±10.4	28.75±15.95	14.15
WBC(X10^3/µL)	11.9±4.0[a]	9.5±8.8	7.4

n-number of participants, ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, ALP-Alkaline phosphatase, TB- Total bilirubin, DB-Direct bilirubin, and IQR- Interquartile range
Independent-sample Kruskal-Wallis test was used for multi-comparison.
a-p<0.05 when two week compared with one week
b-p<0.05 when three week compared with one week

Titration of typhoid fever cases and liver and renal function test results

Antibody titer has also an impact on the level of liver and renal function tests of typhoid fever patients. AST, ALT, and Creatinine levels of typhoid fever study participants of 1:160 and 320 antibody titres showed statically significant when compared with control study subjects of 1:80 (Table 4, Figure 4).

Table 4: The effect of O-antibody titre on Liver and Renal function tests of typhoid fever patients in Motta General Hospital, Northwest Ethiopia, May to December 2023.

Parameters	1:80 (n=70)	1:160 (n=18)	1:320 (n=2)
	(Median± IQR)	(Median± IQR)	(Median± IQR)
ALT(IU/L)	42.6±51.7[a,b]	75.5±75.22	122.85
AST (IU/L)	50.6±61.83[a,b]	99.7±88.4	139.30
ALP(IU/L)	88.5±63.75[a]	151.5±112.5	199
TB (mg/dl)	0.73±0.89	1.52±1.8	2.46
DB (mg/dl)	0.15±0.27	0.69±1.31	1.28
Creatinine(mg/dl)	1.06±0.7[a,b]	1.16±0.37	1.66
Urea (mg/dl)	28.55±9.92	27.05±19.15	16.20
WBC(X10^3/µL)	11.8±4.1	10.2±6.2	8.1

n-number of participants, ALT-Alanine aminotransferase, AST- Aspartate aminotransferase, ALP-Alkaline phosphatase, TB- Total bilirubin, DB-Direct bilirubin, and IQR- Interquartile range

1. Independent-sample Kruskal-Wallistest was used for multicomparison.
2. a-p<0.05when 1:160 compared with 1:80
3. b-p<0.05when 1:320 compared with 1:80

Figure 3: Box-whisker plot of Liver and Renal function tests of typhoid fever patients by duration of illness in Motta General Hospital, Northwest Ethiopia, May to December 2023.

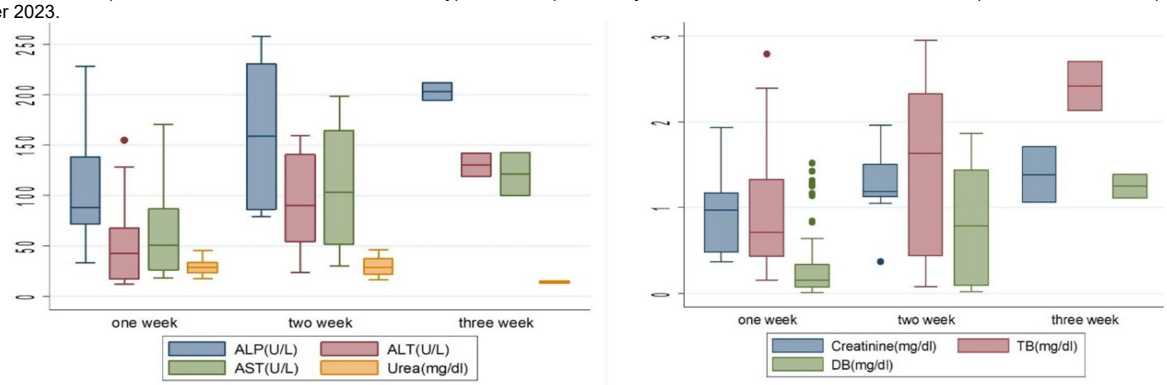
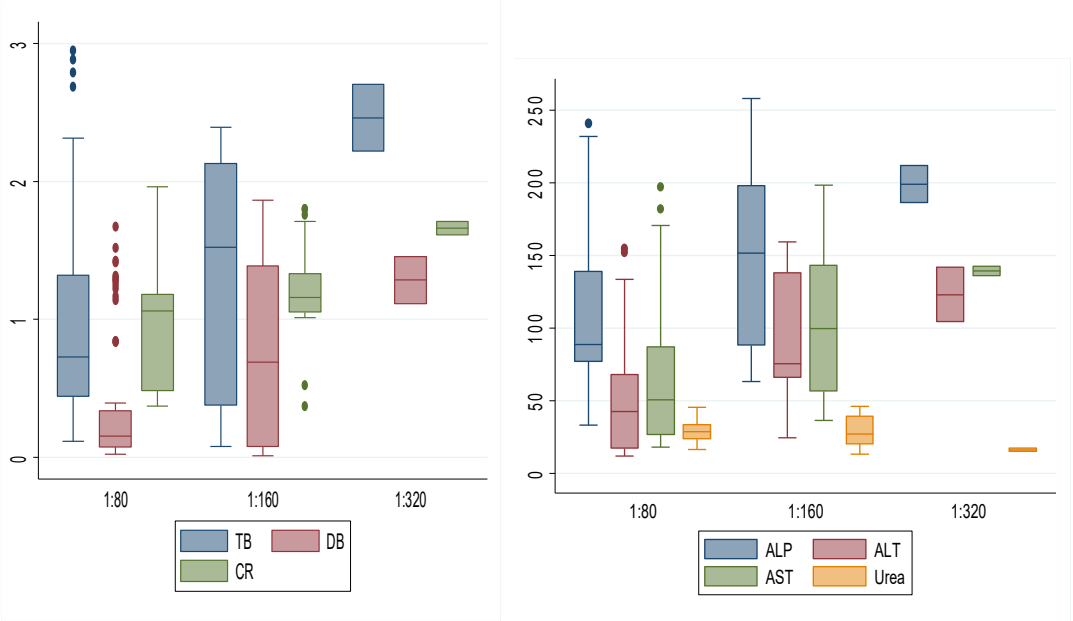


Figure 4: Box-whiskerplot of Liver and Renal function tests of typhoid fever patients by titration at Motta General Hospital, Northwest Ethiopia, May to December 2023.



DISCUSSION

Typhoid fever is a common bacterial infection in the tropics with considerable morbidity and mortality. It mostly affects liver and kidney organs which leads to alteration of liver and kidney function tests[16,17]. According to this study, typhoid fever has a significant impaction the level of liver and renal function tests in comparison to healthy control groups. ALT, AST, ALP, TB, DB, and creatinine are significantly higher in typhoid fever patients as compared to apparently healthy subjects.

Based on these findings the values of AST, ALT, and ALP were significantly higher among typhoid fevers. The finding is in agreement with past studies conducted in Iraq and Cameroon[18,19] which reported significantly higher values of ALT, AST, and ALP in patients with typhoid fever compared to the healthy control groups. Furthermore, different case reports conducted in Malaysia, India, and South Africa support this study and report high levels of ALT, AST, and ALP from TF patients[20-22] also, prospective study in India, across-sectional study conducted in India, and an observational study conducted in the United Arab Emirates showed elevated liver enzymes in typhoid fever patients[23-26].

Similarly, a study conducted in Nigeria[27] reported significantly higher enzyme levels of ALT, AST, and ALP in typhoid fever patients and compared to healthy control groups. This would be due to hepatocyte necrosis, triggered by the volatility of the reactive oxygen species (ROS) from the rupture of the hepatocytoplasmic membrane that is initially used for the dissemination and destruction of Salmonella bacteria in the liver, manifested by high ALT and AST enzymes[28]. Salmonella Typhi exits the intestinal lumen during typhoid fever infection by migrating into lymphoid tissues in the lymphatic circulation, and is subsequently trafficked to liver macrophages (Kupffer cells), where it replicates and disseminates within the body[29]. The lysis of some Salmonella bacteria within the lymph nodes frees the endotoxin (lipopolysaccharides) that ends up in the blood and is transported to the liver. In the liver, kupffer cells are activated by this lipopolisaccharides and secrete cytokines (TNF-α, IFN-γ, IL-1, IL-6, IL-18) that induce to produce of ROS that destroy the Salmonella typhi and also destroy hepatocyte[30]. Serum biochemical parameters of ALT and AST increased with increasing dose of endotoxin during increasing duration of disease[31].

High ALP level suggests that bile ducts may be blocked and that Salmonella typhi serves as an adequate obstruction of bile ducts since it leads to a higher production of ALP by its epithelial cells
and released into circulation of ALP biochemicals[32]. Overall, patients with typhoid fever displayed elevated levels of ALP, AST and ALT correlating to hepatocellular and hepatobiliary impairment which can be the possible effect of endotoxicity affecting the liver parenchyma resulting to oedema and biliary stasis.

TB and DB levels are higher in typhoid fever as compared to healthy controls. Results of this study is similar to the findings of the studies conducted in Cameroon and Nigeria[19,27] it shows that the level of bilirubin was significantly higher in typhoid fever cases when compared with apparently healthy study participants. The liver injury detected through the elevated levels of serum AST, ALT, and ALP were further substantiated through significantly elevated serum bilirubin levels. In typhoid fever patients, the marked serum bilirubin rising shown the liver excretion function disturbance. This could be related to canalicular obstruction by the enlarged hepatocytes[33].

The level of creatinine in typhoid fever elevated in comparison to the healthy subjects in this study is in accordance with the past studies carried out in Nigeria and Cameron[19,34]. The elevation of serum creatinine in typhoid fever may be immunological, or a direct result of the invasion salmonella typhi. The increase in serum creatinine level reflects a reduction in kidney function[35].

In this study, the impact of the duration of illness on the liver and renal parameters of individuals with typhoid fever patients was also analysed. Liver function tests; ALT, ALP, TB, and creatinine levels of TF patients in three weeks and two weeks showed significant increases compared with one week of TF duration, and aspartate transaminase and direct bilirub in levels of TF patients in two weeks showed significant increases compared with one week of TF duration. These findings are similar to the past study conducted in India[23,36].

Strengths and Limitations of the Study

The current study used a fully automated clinical chemistry analyzer for investigating each laboratory test and the study was done with titration and stool antigenic tests. As per the authors' knowledge, this was the first study in Ethiopia. However, the

investigation was constrained by a cross-sectional study unlike a longitudinal study design, which may not show a well-established relationship of liver and renal function test levels between typhoid fever and control Groups. Furthermore, it was conducted with a small sample size which also may not give sufficient information to generalize the whole population.

CONCLUSION AND RECOMMENDATION

Typhoid fever patients showed a significant increment of liver function tests (ALT, AST, ALP, TB, and DB) and renal function tests (creatinine) as compared to control groups. This may indicate that typhoid fever causes an alteration of liver and renal biochemicals. Abnormal liver and renal function tests in typhoid fever are seen more commonly in patients presenting in the 2nd and 3rd week of illness. Based on these findings, the inclusion of liver and renal function tests to other integral laboratory tests for comprehensive diagnosis of typhoid fever is recommended with the consideration of further longitudinal studies by including other liver and renal function test parameters like gamma-glutamyl transferase, albumin, uric acid, electrolytes, lactate dehydrogenase, and C-reactive protein parameters.

Declarations

Ethical approval and consent: This study was approved by the departmental research and ethics review committee of Addis Ababa University Medical Laboratory Science Department with Ref. no. MLS/047/23. An official permission letter was granted from Motta General Hospital administrators. Written informed consent and assent were obtained from the study participants before the commencement of data and specimen collection after the purpose of the study was explained. Confidentiality of participants' information was maintained by employing a special code.

Availability of data: The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: We know of no conflicts of interest associated with the research, authorship and publication of this article.

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Authors contribution

Birku Gashaw, Gobena Dedefo, Samuel Kinde, Mekdes Alem, Abebe Edao Negesso, Derso Wale, and Dr. Mistire Wolde were involved in the design, conception, preparation, and reviewing of the manuscript.

Birku Gashaw, Abera Abreham, Abush Getaneh, Andualem Bayih, Yazal Abay, Melaku Tsegaye, Amanuel Baye, Geleta Gemechu, Woshke Worade, and Dr. Yeshambel Maru coordinating and performing data collection, laboratory work as well as data analysis. Finally, all the authors read and approved the final manuscript.

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Competing interests: The authors declare that there is potentially no conflict of interest related to the article.

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