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Association of Postoperative Hyperbilirubinemia and Infection Among Patients Undergoing Emergency Exploratory Laparotomy for Gastrointestinal Perforation at Tertiary Care Hospital Karachi

Qurrat Ul Ain Arshad[1*], Shireen Sabir Ansari[2], Maida Naeem[3], Shakila Jhatial[4], Maleeha Khan Lodhi[5], Irfan Tariq Keen[6] and Deema Sabtan[7]

[1]Department of Breast Surgery, Liaquat National Hospital, Karachi, Pakistan
[2]Department of General Surgery, Bahria University of Health Sciences, Karachi, Pakistan
[3]Department of General Surgery, Taluka Hospital Digri, Mirpurkhas, Pakistan
[4]Department of Breast Surgery, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[5]Department of Breast Surgery, Liaquat National Hospital, Karachi, Pakistan
[6]Department of Vascular Surgery, Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Karachi, Pakistan
[7]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia

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***Corresponding Author:**
Qurrat Ul Ain Arshad
Department of Breast Surgery, Liaquat National Hospital, Karachi, Pakistan
dr.qa.arshad@gmail.com

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ABSTRACT

Patients presenting to the surgery emergency room complaining of severe abdominal discomfort are often patients with gastrointestinal perforations. In the developing world, there are differences in incidence, site of perforation, aetiology, and demographics. Because of the distinct pathophysiologies associated with elevated levels of direct bilirubin (D-Bil) and indirect bilirubin (I-Bil), the consequences related to these two forms of bilirubin are likewise distinct. **Objectives:** To determine the association of postoperative hyperbilirubinemia and infections among patients undergoing emergency exploratory laparotomy for gastrointestinal perforation at Tertiary Care Hospital, Karachi. **Methods:** This prospective cohort study utilized a non-probability convenience sample in a one-year cohort study that took place at the Department of Surgery, Dr. Ruth K.M. Pfua Civil Hospital in Karachi. The SPSS software (version 26) was used for data processing. The t-test was applied, and the p-value was determined to be less than or equal to 0.05. **Results:** Postoperative infection showed that in the patients who were in the exposed and unexposed groups, 24 (48%) and 15 (30%) had postoperative infection. P-value was 0.006 with a relative risk of 1.60. Mortality showed that in the patients who were in the exposed and unexposed group, 13 (26%) and 02 (4%) had mortality. P-value was 0.001 and a margin of relative risk 6.50. **Conclusions:** The results show that patients with GI perforation who experience postoperative hyperbilirubinemia are more likely to have persistent postoperative infection and have a worse prognosis.

INTRODUCTION

Perforation of the gastrointestinal tract (GIT) is a common medical emergency that is associated with a significant mortality rate (between 30 and 50%) [1]. Acute severe abdominal pain, odynophagia, and vomiting are some of the symptoms that can accompany perforations of the oesophagus, gastric duodenum, and colon, respectively [2]. Perforations of the colon often develop more slowly and can lead to secondary bacterial peritonitis or localized

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abscesses. Some individuals may have delayed symptoms, an abscess that looks like a lump in the abdomen, or sepsis, according to references. Enquire about past episodes of similar pain and any predisposing factors when reviewing a patient's medical history [3-5]. These include things like a history of stomach trauma, foreign bodies in the stomach, peptic ulcer disease, certain medications (especially NSAIDs), and previous surgeries or instrumentation [6]. Many factors can contribute to a bad prognosis, including lower GI tract perforation, advanced age, delayed diagnosis, organ failure, and the presence of comorbid conditions like diabetes and cancer [7]. When organ failure occurs alongside peritonitis or sepsis, the death rate for patients with these conditions increases. Infectious diseases account for the vast majority of ICU deaths [8]. Morbidity in patients with gastrointestinal perforation is also greatly impacted by it. Multiple organ failure may be a risk factor for this condition, which is believed to be partially mediated by inflammatory cytokines [9]. Additionally, bilirubin and bile acid output in the biliary system were both reduced due to biliary tract infection. Serum bilirubin levels tend to rise after invasive surgeries such as cardiopulmonary bypass and esophageal cancer surgeries, which are considered surgical insults [10]. The exact reason for postoperative hepatic injury is yet unknown, although factors such as reduced blood flow to the liver, infections, medications, anesthetic agents, and excessive inflammatory cytokines are thought to have a role [11]. Hyperbilirubinemia can develop after surgery for generalized peritonitis, although little is known about the causes or prognosis for this condition [12].
We aimed to fill the data gap by studying patients in our area who had emergency exploratory laparotomy for gastrointestinal perforation. We wanted to know if there was a correlation between postoperative hyperbilirubinemia and in-hospital outcomes. Early postoperative evaluation of hyperbilirubinemia is crucial since it is a risk factor for poor patient outcomes. This study aimed to determine the association of postoperative hyperbilirubinemia and infections among patients undergoing emergency exploratory laparotomy for gastrointestinal perforation at Tertiary Care Hospital, Karachi.

METHODS

This prospective cohort study utilized a non-probability convenience sample and was conducted at the Department of Surgery, Dr. Ruth K.M. Pfua Civil Hospital in Karachi from July 2021 to July 2022. The study was approved by the Research Evaluation Unit of, College of Physicians and Surgeons of Pakistan (Ref. No. CPSP/REU/SGR/2017-183-9254). The study used a non-probability convenience sampling technique. The 95% two-sided significance level (1-alpha) and 95% power were used for the computation of the sample size. Mortality in the exposed group was 59% and 4% in the unexposed group [13]. The total sample size calculated was 26 (13 in each group). To overcome non-responders and incomplete responses, we have added 50 patients in each group, for a total of 100 patients in this study. Inclusion criteria consisted of patients undergoing emergency exploratory laparotomy for gastrointestinal perforation were included, and patients developing hyperbilirubinemia were grouped into the exposed group, and those who did not develop hyperbilirubinemia were grouped in the unexposed group, either gender having age of 30-70years. Participants who did not give their informed consent were not included in the study. Neither were patients who had a recent infection (such as pneumonia, UTI, or cellulitis), those who had hypothyroidism or hyperthyroidism in their medical history, anyone with a preexisting condition that can hinder thyroid function, such as a history of stroke, renal impairment, COPD, asthma, cirrhosis of the liver, heart failure, or any other similar illness. Each patient's signed informed consent was obtained before any data was gathered. We collected basic demographic information (gender, age, and residency status) from the past. When participants were first included in the study following surgery, A wall-mounted scale was used to measure their height in meters, and a weighing machine was used to measure their weight to the closest kilogramme. A person's BMI was subsequently determined. Patients with and without postoperative hyperbilirubinemia after emergency exploratory laparotomy for gastrointestinal perforation (confirmed on abdominal x-ray showing right upper quadrant sub diaphragmatic free air) were evaluated by the presence of any one or more of the following postoperative outcomes: Postoperative infection: Patients with deep infections affecting structures deeper than the fascial and muscular layers, organ/space infections affecting structures deeper than the skin and subcutaneous tissue, or superficial infections involving the skin and subcutaneous tissue infection that develops within seven days after surgery together with any of the following was classified as postoperative infection. Fever (>38°C), Localized pain (VAS >2), Erythema (red area apparent on clinical examination) and purulent drainage from the skin incision site. Mortality: Patients were followed till discharge and if death occurred within 7 days of surgery it was labeled as mortality using Clavien–Dindo (CD) grades V. Patients undergoing emergency exploratory laparotomy for gastrointestinal perforation and developing serum bilirubin ≥5mg/dl within 48 hours of surgery were labeled postoperative hyperbilirubinemia. Patients undergoing emergency exploratory laparotomy for gastrointestinal

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perforation and developing postoperative hyperbilirubinemia within 48 hours of surgery were labeled as the exposed group, and those who did not develop postoperative hyperbilirubinemia within 48 hours of surgery and during hospital stay were labeled as the unexposed group. Input and analysis were carried out using SPSS version 26.0. Means and standard deviations were computed for continuous variables such as age, height, weight, body mass index, and surgery time. Frequencies and percentages were calculated for categorical factors like gender. A statistically significant result was determined by comparing the two groups using a t-test, where a p-value less than 0.05 was employed. After stratification (with projected frequencies fewer than 5), a chi-square test was utilized; a p≤0.05 was deemed statistically significant, and the relative risk was calculated.

RESULTS

The present study showed descriptive statistics of the exposed and unexposed groups, whereas in both groups, patients' ages ranged from thirty to seventy years. With a standard deviation of ±6.24, the average age of patients in the exposed group was 47.21 years. In contrast, the average time spent in surgery was 2.28±1.47 hours, the average body mass index was 29.58±3.97 kg/m2, the average height was 147±4.21 cm, and the average weight was 71.7±7.25 kg. Like the exposed group, the unexposed group had 50 patients with an average age of 52.48 years and a standard deviation of ±8.41. On the other hand, the average time spent in surgery was 2.16±1.71 hours, the average body mass index was 30.14±2.51 kg/m2, the average height was 158±5.28 cm, and the average weight was 78.7±9.87 kg (Table 1).

Table 1: Descriptive Statistics of the Exposed and Unexposed Groups

Variables	Exposed Group (Mean ± SD)	Unexposed Group (Mean ± SD)	Range (Min-Max)
Age (Years)	47.21 ± 6.24	52.48 ± 8.41	30-70
Duration of surgery (Hours)	2.28 ± 1.47	2.16 ± 1.71	1-4
BMI (Kg/m^2)	29.58 ± 3.97	30.14 ± 2.51	26-34
Height (Cm)	147 ± 4.21	158 ± 5.28	138-172
Weight (Kg)	71.7 ± 7.25	78.7 ± 9.87	68-115

Out of 50 patients in the exposed group, 39 (78%) were male and 11 (22%) were female, according to the frequency distribution of gender. In the unexposed group, however, 41 (82%) were male and 09 (18%) were female. The results showed that out of 50 patients in the exposed group, 30(60%) lived in an urban area, while 20(40%) lived in a rural area. In contrast, 28(56%) of the unexposed group's patients were from urban areas, and 22(44%) were from rural areas. In the exposed group, 14 people (28%) had type II diabetes mellitus, whereas 36 people (72%) did not; in the unexposed group, 8 people (16%) had type II diabetes, and 42 people (84%) did not. Similarly, 18 people (36%) in the exposed group experienced hypertension, while 32 people (64%) did not. Despite this, hypertension was present in 9 cases (18%) and non-existent in 41 cases (82%). In the exposed group, 19 people (or 38% of the total) smoked, while 31 people (or 62% of the total) did not. In contrast, 24 (48%) and 26 (52%), respectively, of the 50 patients in the unexposed group smoked and did not smoke (Table 2).

Table 2: Demographic Characteristics in Exposed and Unexposed Groups

Variables	Exposed Group	Unexposed Group
Male	39 (78%)	41 (82%)
Female	11 (22%)	09 (18%)
Urban Residence	30 (60%)	28 (56%)
Rural Residence	20 (40%)	22 (44%)
Diabetes Mellitus Type II (Yes)	14 (28%)	8 (16%)
Diabetes Mellitus Type II (No)	36 (72%)	42 (84%)
Hypertension (Yes)	18 (36%)	9 (18%)
Hypertension (No)	32 (64%)	41 (82%)
Smoking (Yes)	19 (38%)	24 (48%)
Smoking (No)	31 (62%)	26 (52%)

Assessment of postoperative infection showed that in the patients who were in the exposed and unexposed groups, 24 (48%) and 15 (30%) had postoperative infection. (p=0.006) and relative risk was 1.60. Frequency of mortality showed that in the patients who were in the exposed and unexposed group, 13 (26%) and 02 (4%) had mortality (p=0.001), where a relative risk was 6.50 (Table 3).

Table 3: Postoperative Infection and Mortality in the Exposed and Unexposed Groups

Variables	Exposed Group	Unexposed Group	p-value	Relative Risk
Mortality				
Yes	13 (26%)	02 (4%)	0.001	6.50
No	37 (74%)	48 (96%)		
Postoperative Infection				
Yes	24 (48%)	15 (30%)	0.006	1.60
No	26 (52%)	35 (70%)		

Stratification for age with respect to postoperative infection showed that in the patients who were in 30-50 years age group 18 (36%) and 13 (26%) had postoperative infection in the expose and unexposed group accordingly (p-value 0.002) and relative risk was 1.91 and in patients who were in 51-70 years age group 06 (12%) and 02 (4%) in the expose and unexposed group had postoperative infection respectively (p-value 0.034). with a relative risk of 0.56. Stratification for gender with respect to postoperative infection showed that in the patients who were in male group 17 (34%) and 10 (20%) had postoperative infection in

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the expose and unexposed group respectively (p-value 0.006) and those who were in female group 07 (14%) and 05 (10%) in the expose and unexposed group had postoperative infection respectively (p-value 0.071) having relative risk was 1.14 (Table 4).

Table 4: Postoperative Infection in The Exposed and Unexposed Groups According to Age and Gender

Variables	Exposed Group		Unexposed Group		p-value	Relative Risk
	Yes (%)	No (%)	Yes (%)	No (%)		
Age (Years) 30-50	18 (36%)	16 (32%)	13 (26%)	34 (68%)	0.002	1.91
51-70	06 (12%)	10 (20%)	02 (4%)	01 (2%)	0.034	0.56
Male	17 (34%)	22 (44%)	10 (20%)	31 (62%)	0.006	1.78
Female	7 (14%)	4 (8%)	5 (10%)	4 (8%)	0.071	1.14

The exposed group demonstrated higher postoperative infection (48% vs. 30%) and substantially higher mortality (26% vs. 4%) compared to the unexposed group. Relative risk estimates indicate a 1.60-fold increased risk of postoperative infection and a 6.50-fold increased risk of mortality among patients with hyperbilirubinemia (Table 5).

Table 5: Hyperbilirubinemia and Postoperative Outcomes

Group	Number of Patients	Postoperative Infection (%)	Mortality (%)	Relative Risk for Infection	Relative Risk for Mortality
Exposed Group	50	24 (48%)	13 (26%)	1.60	6.50
Unexposed Group	50	15 (30%)	02 (4%)	N/A	N/A

DISCUSSIONS

The results on the topic of postoperative hyperbilirubinemia and its relationship with poor outcomes are consistent with the findings of other clinical studies. Just like previous reports [14], postoperative hyperbilirubinemia is common in the aftermath of emergency gastrointestinal surgery and is more exaggerated among patients with sepsis or systemic inflammatory reactions. In those patients who developed postoperative hyperbilirubinemia, there were increased infections and increased length of stay, and this is consistent with findings in earlier clinical cohorts [3]. Gastrointestinal perforations cause a high number of acute abdomen emergencies, and may be secondary to a wide range of diseases, trauma, diagnostic or treatment procedures [15]. Gastrointestinal perforations have a high mortality and morbidity rate because of the various complications they may cause, such as septicaemia, diffuse peritonitis, metabolic and circulatory instabilities, renal failures, as well as pulmonary insufficiency. Such complications are aggravated by the variables, including old age and lag in the treatment procedures. Postoperative hyperbilirubinemia is one of the frequent postoperative complications and is associated with poor prognosis [16]. The total bilirubin is based on two factors: direct bilirubin (D-Bil) and indirect bilirubin (I-Bil). Symptoms of hepatocyte excretory failure include cholestasis in the case of sepsis, hypoxic hepatocyte damage, and drug-induced hepatic injury, which is indicated by high D-Bil. The other ailments associated with high levels of I-Bil include haemolysis and blood transfusion reactions. D-Bil and I-Bil can be linked to clinical outcomes differently because they have different pathophysiologies [17]. Patients in the exposed group had 24 (48%) and those in the unexposed group had 15 (30) cases of postoperative infection (p=0.006). Death used in 13 (26%) out of the exposed group and 2 (4) out of the unexposed group. It has also been reported that the prevalence of postoperative infection (77% vs 9%) and mortality (59% vs 4) in patients developing as opposed to not developing postoperative hyperbilirubinemia [18]. The potential causes of postoperative hyperbilirubinemia may include surgical injury, infection, too much bleeding, transfusion, and natural liver dysfunction after major surgery. Patients subjected to thoracic surgery on the esophagus even without infection can have an elevation in their levels of blood bilirubin and inflammatory cytokines post-surgery as a result of surgical shock. One trial demonstrated perioperative steroids as reducing this effect. It has been postulated that metabolism of bilirubin is altered and increased following major operations. Factors linked to postoperative hyperbilirubinemia in the scenario of generalized peritonitis as a result of gastrointestinal perforation included advanced age, poor nutritional condition, decreased base loss, postoperative infection, delay before surgery, greater serum total bilirubin level preoperative, and longer time delay preoperative [19]. The relationship between serum bilirubin level in the preoperative period and the time interval between perforation and surgery, and the fact that the incidence of predisposing liver illnesses in both groups was similar, provides evidence that the advanced form of peritonitis was the cause of elevated serum bilirubin level before surgery [11]. Poor nutrition before elective surgery predisposes one to the occurrence of complications following the surgery. This would result in a high morbidity and mortality rate in the form of relative increases in bacterial and surgical insults, poor nutrition, old age, and delays between perforation and surgical operation. Patients who experienced preoperative shock (P<0.001) had higher levels of lactic dehydrogenase and aspartate aminotransferase at the preoperative stage, which means that inadequate systemic circulation is the probable cause, but not the exact cause. These research findings support previous studies that relate postoperative infection to hyperbilirubinemia and mortality [20]. Hyperbilirubinemia patients suffered a higher mortality rate (59%) as

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compared to their counterparts (4%). During the three to five days post-surgery, the level of blood bilirubin decreased in hyperbilirubinemia patients who survived, but it was stable in those who died. The following factors were found to increase the postoperative mortality probability: hyperbilirubinemia (p<0.001), postoperative infection (p=0.005), preoperative shock (p=0.003), and decreased platelet count (p=0.015) [21, 22]. The mortality rate of gastroduodenal perforation reported in most studies is approximately 5%-6% which has ranged between 0-18. The 30-day mortality rate of gastric cancer-induced perforation was between 7% and 20%, whereas that of colorectal perforation, the most adverse outcome, was between 12% and 22%. The outcomes of this research (16%) cannot be significantly different from these numbers [2]. Advanced age, postoperative shock, delayed surgery, and the conditions of comorbidity with severe illnesses like diabetes or renal failure are considered adverse prognostic factors of gastroduodenal and colorectal perforations.

The use of a non-probability convenience sample may introduce selection bias and limit the generalizability of the findings. Additionally, the relatively short follow-up period restricted assessment of long-term postoperative outcomes and complications. Future studies with larger, randomly selected cohorts and extended follow-up are recommended to validate these findings and evaluate long-term postoperative effects.

CONCLUSIONS

Factors associated with hyperbilirubinemia in the setting of generalised peritonitis caused by gastrointestinal perforation include advanced age, poor nutritional status, a reduction in the base excess, a length of time until surgical intervention, and complications following surgery related to infection. There was an increased risk of complications and death for patients who developed postoperative hyperbilirubinemia. Improving surgical infection control is crucial, as these findings indicate a clear correlation between postoperative hyperbilirubinemia and infection and poor prognosis in patients with GI perforation. Postoperative hyperbilirubinemia was significantly associated with postoperative infection and prolonged hospitalization, suggesting its potential role as a marker of disease severity and postoperative stress response, rather than a proven independent predictor.

Authors' Contribution

Conceptualization: QUAA
Methodology: QUAA, MN
Formal analysis: QUAA, SSA
Writing and Drafting: SJ, MKL, ITK, DS
Review and Editing: QUA, SSA, MN, SJ, MKL, ITK, DS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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