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Evaluation of Blood Lactate Level as a Predictor of In-hospital Morbidity and Mortality in Patients undergoing Surgery for Bowel Perforation: A Prospective Cohort Study

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ABSTRACT

Introduction: Perforation peritonitis is associated with significant Morbidity and Mortality (M&M). The predictive performance of blood lactate levels and their clearance varies depending on the timing of measurement, and the optimal time for measurement remains unclear.

Aim: To evaluate perioperative lactate levels and their clearance as predictors of in-hospital M&M in bowel perforation surgery.

Materials and Methods: The present prospective cohort study was conducted in the Department of Anaesthesiology and Critical Care, Pt. BD Sharma PGIMS, Rohtak, Haryana, India, from March 2023 to December 2023. Study was conducted on 40 adult patients undergoing surgery for bowel perforation, and clinical and various laboratory parameters were observed from admission until discharge. Baseline and perioperative lactate levels were recorded up to 24 hours postoperatively. The association of M&M with different scores such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Mannheim Peritonitis Index (MPI), as well as, lactate levels and lactate clearance, was assessed. The diagnostic accuracy of lactate levels and lactate clearance at different time points in the perioperative period to predict M&M was calculated, and finally, the 'Bidirectional Stepwise Selection' (BSS) was used to select the most useful predictor of M&M.

Results: Total 40 participants were included in the study, of which 34 were males and 6 were females. The overall M&M rates were 50% and 30%, respectively. On univariate analysis, there was a significant difference between non survivors and survivors in terms of age (50.92 vs 38.07 years, p-value=0.004), APACHE II score (10.00 vs 6.46, p-value=0.028), preoperative serum creatinine (1.41 vs 1.13 mg/dL, p-value=0.043), 24-hour postoperative lactate (4.75 vs 1.54 mmol/L, p-value=0.005), and lactate clearance (-28.97 vs 24.83%, p-value=0.03). Patients with or without morbidity showed a significant difference in age (47.7 vs 36.15 years, p-value=0.005), MPI score (22.45 vs 18.6, p-value=0.048), preoperative serum creatinine (1.40 vs 1.03 mg/dL, p-value=0.028), and 24-hour postoperative lactate (3.65 vs 1.35, p-value=0.002). In BSS analysis, age and 24-hour postoperative lactate were identified as good predictors of M&M, with the latter being the best predictor.

Conclusion: The incidence of M&M is quite high in perforation peritonitis. Among all predictors, 24-hour postoperative lactate is the strongest predictor of M&M and may be useful in risk stratification and optimising treatment accordingly.

Keywords: Acute physiology and chronic health evaluation II, Gastrointestinal perforation, Mannheim peritonitis index, Peritonitis, Postoperative, Sequential organ failure assessment

INTRODUCTION

Perforation peritonitis is associated with significant perioperative M&M. An overall mortality rate of 17.86% has been observed in the Indian population [1]. Rapid resuscitation and early administration of broad-spectrum antibiotics, along with appropriate source control, are recommended for the management of these patients [2]. The M&M in Gastrointestinal (GI) perforation surgery depends on various factors, such as age, the physiological condition of the patient, the extent of the disease, and the timing of the intervention [1]. Various scoring systems, including APACHE II, SOFA and MPI, have been studied as predictors of prognosis in these patients; however, the results are variable, and blood lactate (Lac) levels were not included in these scoring systems [3-5].

In cases of perforation peritonitis, bowel ischaemia, combined with septicaemia or septic shock, can lead to increased production and decreased clearance of Lac. Therefore, measuring baseline Lac, which reflects the degree of disease severity, and monitoring its trend over time during management may help in predicting M&M. The predictive performance of Lac and Lactate Clearance (LC) varies depending on the timing of measurement in the perioperative period. Some authors have found that postoperative Lac is a better predictor, but the timing of measurement in the postoperative period has been variable [3-6]. Thus, the optimal time to measure lactate remains unclear, as its concentration may vary significantly during the perioperative period due to complex pathophysiology [7]. Consequently, the present study was conducted to evaluate the role of baseline and perioperative blood lactate levels and their clearance as independent predictors of M&M in patients undergoing surgery for bowel perforation.

The primary objective of the present study was to evaluate baseline and perioperative Lac and LC as predictors for in-hospital M&M in bowel perforation surgery. The secondary objectives were to observe the incidence of in-hospital M&M and to evaluate and compare other scoring systems, such as APACHE II, SOFA and MPI, as predictors of M&M.

MATERIALS AND METHODS

The present prospective cohort study was conducted in the Department of Anaesthesiology and Critical Care, Pt. BD Sharma PGIMS, Rohtak, Haryana, India, from March 2023 to December 2023, after obtaining approval from the Institutional Ethics Committee

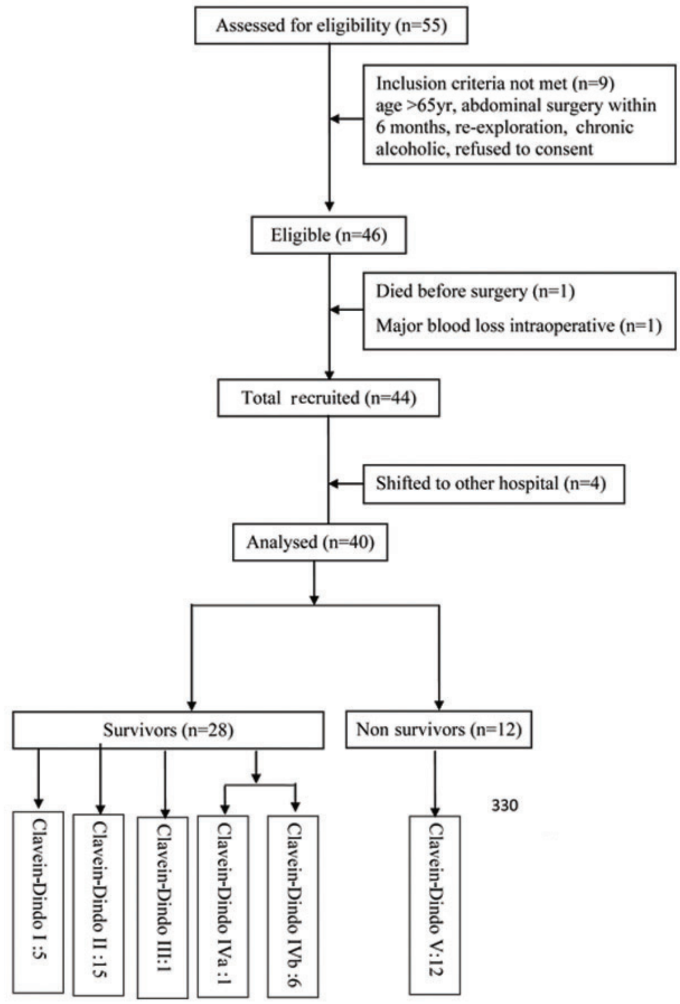
(EC/NEW/INST/2022/HR/0189) and registering with the Clinical Trial Registry of India (CTRI/2023/03/050727). The study adheres to the ethical standards of the Helsinki Declaration, and informed consent was obtained from each patient.

Sample size calculation: The sample size was calculated using the Area under the Receiver Operating Characteristic Curve (AUROC) to predict 28-day mortality using preoperative lactate levels, which was found to be 0.86 according to the reference study by Jobin SP et al., [4]. The required sample size, at 95% power and an alpha error of 0.05, was determined to be 20. An approximate proportion of outcome-positive and negative groups was considered to be 1:1. To account for potential loss to follow-up, the final minimum sample size was set at 26, ensuring an equal number of positive and negative subjects. However, a total of 40 patients were enrolled based on the availability of perforation cases during the study period at the study Institute.

Inclusion criteria: Patients of both sexes, aged between 18 years and 65 years with American Society of Anaesthesiologists (ASA) grades 1-3 (E), undergoing surgery for bowel perforation under General Anaesthesia (GA) were included in the study.

Exclusion criteria: Patients with significant cardiac, renal, pulmonary and hepatic diseases, diabetic ketoacidosis, those on biguanides, pregnant patients, individuals with major blood loss or massive transfusion, a history of any major illness or Intensive Care Unit (ICU) stay in the last six months, re-exploration laparotomy, iatrogenic bowel perforation, chronic alcohol intake, and patients who refused to participate were excluded from the study.

A total of 55 patients were assessed for eligibility, but nine patients were excluded due to various exclusion criteria. Out of the 46 eligible patients, one patient expired before surgery, and one experienced major intraoperative blood loss. Forty-four patients were recruited, but four patients were transferred to other hospitals during the course of treatment; ultimately, 40 patients were analysed [Table/Fig-1].



[Table/Fig-1]: Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

Study Procedure

The demographic data, detailed history, routine investigations and pre-resuscitation baseline Arterial Blood Gas (ABG) analysis (Stat Profile® pHOx® Ultra by Nova Biomedical) samples taken from the radial or femoral artery were recorded. Different scores (MPI, APACHE II, and SOFA) were calculated using an online calculator (mdcalc.com) based on preoperative examinations and intraoperative details [8-10].

Resuscitation in the Emergency Department was performed using a balanced salt solution (initial bolus up to 30 mL/kg within 3 hours of admission) based on clinical signs of dehydration, such as the straight leg raising test and observation for fluid overload, to maintain Mean Arterial Pressure (MAP) ≥65 mm Hg with adequate Urine Output (U/O) (0.5-1 mL Kg^{-1} h^{-1}). Since no differences in terms of mortality have been observed with different methods of fluid resuscitation (restrictive vs liberal), after the initial bolus, the authors administered fluid in small boluses of 250-500 mL with haemodynamic monitoring to avoid fluid overload [11]. Vasopressors were initiated if MAP remained less than 65 mm Hg even after fluid resuscitation. If a patient required a vasopressor, as per the sepsis guidelines, nor epinephrine was used as the first choice, and the same (drug used and its dose) was included in the SOFA score calculation. Broad-spectrum antibiotics (ceftriaxone 1 g every 12 hours/ceftriaxone sulbactam 1.5 g every 12 hours, and metronidazole 500 mg every eight hours intravenously, with amikacin 500 mg every 12 hours added if kidney function and U/O were normal) were initiated within 30-60 minutes of admission. According to the MPI criteria, patients with preoperative creatinine levels >177 mmoL/L, urea levels >167 mmoL/L, or oliguria <20 mL/h were classified as having preoperative Acute Kidney Injury (AKI) [12].

All patients received GA with monitoring according to the standards set by the ASA. Intraoperative fluid was administered based on clinical parameters with the aim of maintaining MAP ≥65 mm Hg and U/O of 0.5-1 mL Kg^{-1} h^{-1} (except in patients with preoperatively decreased U/O, where other methods such as central venous pressure-guided fluid therapy were used). Surgical details, including the site and cause of perforation (malignancy or not), duration of peritonitis, whether peritonitis was diffuse, the procedure performed, and the type of intraperitoneal fluid, were recorded, and based on that, the MPI score was calculated. The intraoperative amount of intravenous fluids infused, U/O, blood loss, and the requirement for blood/blood components and vasopressors were observed. After the completion of surgery, haemodynamically stable patients (maintaining MAP ≥65 mmHg without vasopressors) with adequate respiratory efforts were extubated. Haemodynamically unstable patients or those who required postoperative Mechanical Ventilator support (MV) were transferred to the ICU for further management and were followed accordingly. ABG was performed at the time of admission (baseline), post-resuscitation, in the immediate postoperative period, and 24 hours postoperatively. Baseline ($Lac_{baseline}$), preoperative after resuscitation (Lac_{preop}), immediate postoperative ($Lac_{immed\ postop}$), and 24 hours postoperative ($Lac_{24\ h\ postop}$) lactate levels were recorded. Based on lactate levels, different LCs values such as post-resuscitation ($LC_{post\ resuscitation}$), immediate postoperative ($LC_{immed\ postop}$), and at 24 hours postoperatively ($LC_{24\ h\ postop}$) were calculated using the formula (lactate initial-lactate delayed) / lactate initial×100 [13].

Daily postoperative monitoring was conducted to assess for any surgical complications, the need for vasopressor support, respiratory support or failure {Partial pressure of arterial Oxygen (PaO_2)/Fraction of inspired Oxygen (FiO_2) <300, the need for oxygen therapy, or mechanical ventilation support}, kidney function, the requirement for dialysis, parenteral or enteral nutrition and any other organ dysfunctions. The duration of hospital stay and in-hospital M&M were recorded. Postoperative morbidity was calculated using the Clavien-Dindo (CD) grading system for surgical complications [14]. Based on morbidity, patients were divided into two groups: those with major complications (CD grade ≥3) and those without major complications (CD grade <3). Additionally, patients were categorised based on mortality into survivor and non survivor groups.

STATISTICAL ANALYSIS

The incidence of mortality and morbidity was recorded. Baseline and perioperative blood lactate levels were considered as screening tests. Descriptive analysis was performed using mean and standard deviation for quantitative variables, and frequency and proportion for categorical variables. The association between outcomes (survivor, non survivor, with major complications, and without major complications) and quantitative variables was assessed by comparing mean values using the t-test (for normally distributed data) or the Wilcoxon-Mann-Whitney test (for non normally distributed data). For categorical variables, Fisher's exact test or the Chi-squared test was used. Diagnostic accuracy, AUC, 95% CI and p-values were assessed to predict M&M using lactate and lactate clearance by constructing an ROC curve. An effort was made to identify the appropriate cut-off values of the scores for risk stratification using the Youden Index. Finally, 'BSS' was employed to select only the most useful variables. Data analysis was conducted using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) software version 25.0.

RESULTS

The analysis included a total of 40 patients. The mortality rate was 30%, and the morbidity (CD grade ≥3) was 50%. Postoperative morbidity grading showed that CD grade 1 occurred in 5 (12.5%) patients, CD grade 2 in 15 (37.5%) patients, grade 3 in 1 (2.5%) patient, grade 4a in 6 (15%) patients, grade 4b in 1 (2.5%) patient, and grade 5 in 12 (30%) patients.

Non survivors, when compared to survivors, had higher age, APACHE II scores, preoperative serum creatinine levels, 24-hour postoperative lactate levels and lactate clearance [Table/Fig-2]. Patients with major complications (CD grade ≥3) exhibited higher age, MPI scores, preoperative serum creatinine levels and 24-hour postoperative lactate levels compared to patients without major complications [Table/Fig-2]. No significant difference in morbidity and mortality was observed regarding the mean duration from the onset of symptoms to surgery and from admission to surgery [Table/Fig-3].

All but two patients were operated on within 24 hours of admission; both of these patients survived, although one experienced major

	Morbidity CD grade ≥3			Mortality		
Parameters	No (n=20)	Yes (n=20)	p-value, test	No (n=28)	Yes (n=12)	p-value, test
Age (years) (mean±SD)	36.15±14.74	47.70±9.59	0.005* W	38.07±13.33	50.92±9.66	0.004*W
Gender (M/F%)	17/3 (85/15%)	17/3 (85/15%)	1.000 F	24/4 (85.7/14.3%)	10/2 (83.3/16.7%)	1.000 F
Weight (kg)	58.70±6.89	62.15±8.08	0.155 T	61.14±8.10	58.75±6.36	0.292 W
ASA grade 1/2/3 (E)	9/11/0 (45/55%)	8/10/2 (40/50/10%)	0.585 F	10/17/1 (35.7/60.7/3.6%)	7/4/1 (58.3/33.3/ 8.3%)	0.235 F
Haemoglobin (g/dL)	13.70±2.66	13.32±2.06	0.617 T	13.55±2.55	13.44±1.94	0.712 W
Serum albumin (g/dL)	3.10±0.83	2.62±0.50	0.071 W	2.92±0.79	2.71±0.48	0.625 W
TLC (/mm³) <4000, 4-11000, >11000	1,13,6 (5, 65, 30%)	4,11,5 (20, 55, 25%)	0.438 F	2,19,7 (7.1, 67.9, 25%)	3, 5, 4 (25, 41.7, 33.3%)	0.170 F
Serum creatinine (mg/dL)	1.03±0.31	1.40±0.66	0.028* W	1.13±0.53	1.41±0.55	0.043* W
Preoperative AKI (Yes)	0	2 (10.0%)	0.487 F	1 (3.6%)	1 (8.3%)	0.515 F
Preoperative Vasopressor (Yes)	0	1 (5.0%)	1.000 F	0	1 (8.3%)	0.300 F
Preoperative MV (Yes)	0	0	1.000 C	0	0	1.000 C
I/O diff. during resuscitation (mL/kg)	24.67±6.49	29.28±16.70	0.715 W	27.70±14.41	25.28±7.70	0.605 W
SOFA	1.80±1.01	2.25±1.62	0.549 W	1.71±1.01	2.75±1.76	0.080 W
APACHE II	6.40±3.52	8.65±5.21	0.282 W	6.46±3.88	10.00±5.13	0.028* W
MPI	18.60±5.99	22.45±5.51	0.048* W	19.96±6.36	21.83±5.10	0.332 W
Lactate (mmol/L) (admission)	2.54±1.80	3.68±2.54	0.172 W	3.22±2.26	2.84±2.29	0.565 W
Lactate (mmol/L) (preoperative)	2.20±1.24	3.19±2.44	0.151 W	2.53±1.47	3.09±2.87	0.894 W
Lactate (mmol/L) (Immediate postoperative)	2.12±1.23	3.41±2.61	0.051 W	2.60±1.82	3.15±2.76	0.616 W
Lactate (mmol/L) 24 h (postoperative)	1.35±0.80	3.65±4.25	0.002* W	1.54±0.82	4.75±5.25	0.005* W
Lactate clearance (postresuscitation)	-0.57±43.00	5.59±28.92	0.787 W	7.65±40.14	-9.48±22.21	0.067 W
Lactate clearance (immediate postoperative)	1.65±35.92	0.18±97.61	0.317 W	-5.61±49.84	16.13±110.59	0.941 W
Lactate clearance (24 h postoperative)	21.80±50.38	-4.43±74.47	0.234 W	24.83±45.59	-28.97±85.31	0.030* W

[Table/Fig-2]: Association of demographics and preoperative parameters with Morbidity and Mortality (M&M).
Values are expressed in mean±SD or n (%); W: Wilcoxon-Mann-Whitney U test; F: Fisher's exact test; C: Chi-squared test; T: t-test; CD grade: Clavien-Dindo grade; *Significant at p-value <0.05; M/F: Male/female; ASA: American society of anesthesiologists; E: Emergency surgery; TLC: Total leukocyte count; AKI: Acute kidney injury; MV: Mechanical ventilation; I/O: Input-output; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation; MPI: Mannheim peritonitis index

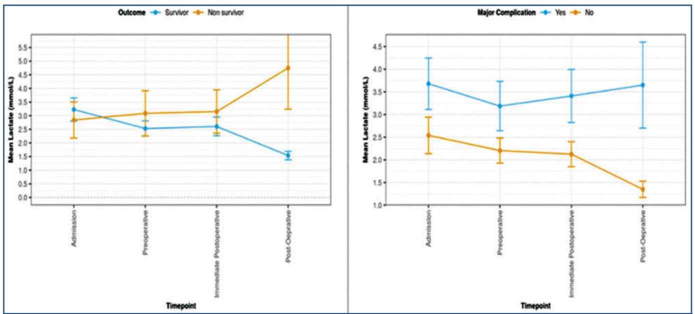
	Morbidity CD grade ≥3			Mortality		
Parameters	No (n=20)	Yes (n=20)	p-value, test	No (n=28)	Yes (n=12)	p-value, test
Site of perforation	n=20	n=19	0.605 F	n=28	n=11	0.157 F
Stomach	7 (35.0%)	6 (31.6%)	-	10 (35.7%)	3 (27.3%)	-
Small intestine	12 (60.0%)	11 (57.9%)	-	17 (60.7%)	6 (54.5%)	-
Duodenum	0 (0%)	1 (5.26%)	-	0 (0%)	1 (9.09%)	-
Jejunum	4 (20%)	2 (10.53%)	-	5	1 (9.09%)	-

Duodenum+jejunum	0	1 (5.26%)	-	0	1 (9.09%)	-
Ileum	8 (40%)	7 (36.84%)	-	12	3 (27.27%)	
Appendix	1 (5.0%)	0	-	1 (3.6%)	0	-
Large intestine	0	2 (10.5%)	-	0	2 (18.2%)	-
Malignant cause (Yes)	0	0	1.000 C	0	0	1.000 C
Contaminated ascites (Yes)	19 (95.0%)	18 (90.0%)	1.000 F	27 (96.4%)	10 (83.3%)	0.209 F
Blood loss (mL)	235.50±79.57	316.00±172.85	0.082 W	256.79±101.00	320.00±200.86	0.350 W
Blood transfusion (Yes)	13 (65.0%)	15 (75.0%)	0.490 F	20 (71.4%)	8 (66.7%)	1.000 F
Urine output (mL)	457.50±351.01	496.50±383.49	0.516 W	449.29±317.34	541.67±463.17	0.585 W
I/O difference (mL/Kg)	32.30±11.72	37.16±19.71	0.351 T	33.60±11.05	37.36±24.87	0.825 W
Intraoperative vasopressors (Yes)	0	6 (30.0%)	0.020* F	2 (7.1%)	4 (33.3%)	0.055 F
eTime (a) (h)	118.45±159.29	104.25±94.04	0.559 W	112.86±143.67	107.83±92.74	0.486 W
eTime (b) (h)	8.05±6.66	16.93±28.29	0.255 W	14.62±24.55	7.51±3.51	0.894 W
Duration of surgery (Min)	153.85±46.74	179.00±53.57	0.122 T	162.04±44.64	176.67±65.20	0.824 W
Postoperative MV	0	10 (52.6%)	<0.001 F	4 (14.3%)	6 (50.0%)	0.017 F
Postoperative vasopressors	0	7 (35.0%)	0.008* F	1 (3.6%)	6 (50.0%)	0.001* F
Postoperative AKI/dialysis	0	2 (10%)	0.151 C	0	2 (16.67%)	0.0286* C
Duration of ICU stay (h)	18.00±80.50	98.05±102.93	<0.001* W	49.29±111.73	78.42±63.46	0.003* W
Duration of hospital stay (Days)	11.65±5.74	20.75±27.89	0.892 W	20.04±23.32	7.25±4.05	0.001* W

[Table/Fig-3]: Association of intraoperative and postoperative parameters with mortality and morbidity.
Values are expressed in mean±SD or n (%); W: Wilcoxon-Mann-Whitney U test; F: Fisher's exact test; C: Chi-squared test; T: t-test; CD grade: Clavien-Dindo grade; *Significant at p-value <0.05; I/O: Input-output, AKI: Acute kidney injury; eTima (a): Duration from onset of symptoms to surgery; eTime (b) Time from admission to surgery; MV: Mechanical ventilation

complications. No differences were noted in terms of the site of perforation, intraoperative blood loss, blood transfusion, urine output, input/output difference, or duration of surgery [Table/Fig-3]. Various surgical procedures were performed, including Graham patch repair (14 patients), jejunojejunal anastomosis (5 patients), ileostomy (15 patients), band excision (2 patients), perforation repair with hemicolectomy (1 patient), transverse colon anastomosis (1 patient), and end sigmoid colostomy with Hartmann procedure (1 patient), based on the site of perforation.

The trend of lactate levels in the survivor group showed a significant decrease (p-value <0.001), while in the non survivor group, lactate levels significantly increased (p-value=0.005) from admission to 24 hours postoperatively [Table/Fig-4]. In patients without major complications, there was a significant decrease (p-value=0.006) in lactate levels from admission to 24 hours postoperatively. In contrast, the decrease in lactate levels over time in the group with major complications was minimal (p-value=0.670) [Table/Fig-4].



[Table/Fig-4]: Change in lactate over time.

In the present study, lactate levels at 24 hours postoperatively (Lac24h postop) demonstrated the highest AUROC of 0.786 and the highest diagnostic accuracy of 88% for predicting mortality at a cut-off level of ≥3.2 mmol/L. To predict morbidity, the AUROC was 0.785, with a diagnostic accuracy of 72% at a cut-off of ≥1.5 mmol/L [Table/Fig-5]. In the final multivariate predictive model using bidirectional stepwise selection, among variables with p-value <0.05 (age, APACHE II score, MPI, preoperative serum creatinine, Lac24h postop and lactate clearance at 24 hours postop); Lac24h postop was identified as the best predictor [Table/Fig-6].

DISCUSSION

In the present study, the overall mortality rate was 30%, and the incidence of morbidity (CD grade ≥3, labelled as a major complication here) was 50%. No relationship between mortality and the site of perforation was observed. Higher age, APACHE II score, preoperative serum creatinine levels, lactate at 24 hours postoperatively ($Lac_{24h\ postop}$) and lactate clearance at 24 hours postoperatively ($LC_{24h\ postop}$) were associated with higher mortality, while morbidity was greater in patients with higher age, MPI score, preoperative serum creatinine levels and $Lac_{24h\ postop}$. Similarly, in other studies, high morbidity was observed after intestinal perforation surgery. [6,15].

Mortality rates vary among different studies, ranging from 10% to 33%, due to differences in prognostic factors such as age,

Variables	Mortality						Morbidity					
	Cut-off	AUC (95% CI)	p-value	Sn (%)	Sp (%)	DA (%)	Cut off	AUC (95% CI)	p-value	Sn (%)	Sp (%)	DA (%)
Lactate (mmol/L) (Admission)	2.3	0.56 (0.36-0.759)	0.185	58.3	64.3	62.5	2.8	0.627 (0.452-0.803)	0.102	50.0	75.0	62.5
Lactate (mmol/L) (Preoperative)	2	0.515 (0.313-0.716)	0.573	66.7	42.9	50.0	1.23	0.634 (0.458-0.809)	0.058	90.0	35.0	62.5
Lactate (mmol/L) (Immediate postoperative)	3.2	0.552 (0.356-0.748)	0.418	41.7	71.4%	62.5	3.1	0.681 (0.514-0.848)	0.047*	50.0	80.0	65.0
Lactate (mmol/L) (24 h postoperative)	3.2	0.786 (0.594-0.977)	<0.001*	66.7	96.4	87.5	1.5	0.785 (0.644-0.926)	0.004*	80.0	65.0	72.5
Lactate Clearance (%) (postresuscitation)	4.35	0.686 (0.522-0.85)	0.018*	83.3	57.1	65.0	21.42	0.526 (0.341-0.712)	0.256	85.0	30.0	57.5
Lactate Clearance % (Immediate postoperative)	66.67	0.509 (0.285-0.733)	0.006*	25.0	100.0	77.5	3.45	0.594 (0.405-0.783)	0.027*	70.0	65.0	67.5
Lactate Clearance (24 h postoperative)	9.09	0.72 (0.523-0.917)	0.013*	66.7	75.0	72.5	28.57	0.611 (0.431-0.791)	0.102	75.0	50.0	62.5

[Table/Fig-5]: Performance of study parameters for predicting mortality and morbidity.
AUC: Area under the curve; 95% CI: Confidence interval; *Significant at p-value <0.05; Sn: Sensitivity, Sp: Specificity; DA: Diagnostic accuracy

Parameters	Mortality			Morbidity (CD grade ≥3)		
	Univariable OR (95% CI, p-value)	Multivariable OR (95% CI, p-value)	Multivariable bidirectional stepwise selection OR (95% CI, p-value)	Univariable OR (95% CI, p-value)	Multivariable OR (95% CI, p-value)	Multivariable bidirectional stepwise selection OR (95% CI, p-value)
Age (years)	1.09 (1.03-1.17, p=0.011)	1.06 (0.98-1.16, p=0.208)	1.07 (1.00-1.16, p=0.057)	1.08 (1.02-1.15, p=0.012)	1.06 (0.99-1.15, p=0.122)	1.06 (1.00-1.13, p=0.065)
APACHE II	1.20 (1.02-1.45, p=0.035)	1.12 (0.80-1.66, p=0.529)	-	1.13 (0.98-1.35, p=0.127)	0.97 (0.76-1.26, p=0.832)	-
MPI score	1.06 (0.94-1.20, p=0.365)	1.03 (0.85-1.27, p=0.775)	-	1.13 (1.01-1.30, p=0.052)	1.07 (0.92-1.26, p=0.398)	-
Serum creatinine (mg/dL)	2.44 (0.71-11.35, p=0.177)	0.68 (0.04-7.85, p=0.762)	-	8.07 (1.39-96.88, p=0.058)	3.75 (0.29-105.61, p=0.382)	-
Lactate (mmol/L) (24 h Postoperative)	2.65 (1.41-6.18, p=0.009)	1.83 (1.03-5.42, p=0.137)	2.36 (1.09-5.10, p=0.030)	2.73 (1.41-6.56, p=0.010)	2.32 (1.02-8.15, p=0.130)	2.53 (1.09-5.85, p=0.031)
Lactate clerance (24 h Postoperative)	0.99 (0.97-1.00, p=0.033)	0.99 (0.97-1.01, p=0.199)		0.99 (0.98-1.00, p=0.208)	1.00 (0.98-1.02, p=0.907)	-

[Table/Fig-6]: Logistic regression analysis for mortality and morbidity with all variables.
OR: Odds ratio; 95% CI: Confidence interval; p: p-value; CD grade: Clavien-Dindo grade; APACHE: Acute physiology and chronic health evaluation; MPI: Mannheim peritonitis index

aetiology and site of perforation, as well as, variations in the time between the onset of symptoms and hospital admission or surgical intervention [3-6,12,15,16]. The spectrum of aetiology for perforation differs between developed and developing countries. In developed countries, malignant causes of lower GI perforation are more frequent, while in developing countries, perforations of the upper GI tract, such as duodenal ulcers and enteric perforations, are more common [17]. The site of perforation may influence the patient's condition and the outcome. In cases of colonic perforation, the dissemination of bacteria can lead to peritonitis, septic shock and multiorgan failure, which are associated with a poor prognosis. In the present study, most patients had small bowel perforation [Table/Fig-3], and unlike other studies, the authors did not find any association between the site of perforation and mortality [5,16].

Authors who have studied pre and postoperative lactate levels for predicting mortality after bowel perforation have reported variable results. Similar to the present study, Lac_{24h} postop showed the highest AUROC and the best sensitivity and specificity for predicting mortality in patients with perforation peritonitis in another study [4]. Some authors found that postoperative lactate levels are better predictors, although the timing of measurement varied [3-6]. Postoperative lactate measured at the end of surgery has been identified as a useful predictor of mortality after intestinal perforation in some studies [3,6]. In another study, both pre and postoperative lactate levels were elevated in non survivors [5]. One author noted that the incidence of postoperative hyperlactatemia was higher in non survivors; however, in multivariate analysis, it was not identified as an independent predictor of mortality [18]. In trauma patients, one study observed an association between a lack of lactate normalisation in the initial 24 hours and lower chances of survival, while other authors did not find such an association; however, admission lactate was linked to the patient's prognosis in that study [19,20].

The authors observed an increase in the incidence of M&M with advancing age [Table/Fig-2]. Other studies have also noted a significant difference in age between survivors and non survivors [4,12,15,16]. However, some studies did not find any significant difference in age, as most of their patients were in the older age group [3,5]. The authors included only ASA 1-3 (E) grade patients to counteract this confounding factor. The authors did not find ASA grading to be a reliable tool for predicting mortality [Table/Fig-2]. Other studies that included higher ASA grades also did not observe any correlation between ASA grades and mortality [6,15]. Similarly, in one study, the APACHE II score was found to be a better predictor than the ASA grade for M&M in patients undergoing emergency laparotomies [21]. In contrast, another study noted that higher ASA grades (4 and 5) were present in the non survivor group [16].

Morbidity and mortality are affected by co-morbidities, but the authors excluded patients with severe diseases. In another study that measured the Charlson co-morbidity index based on co-morbid diseases, no difference was found between survivors and non survivors [5]. Thus, while co-morbidity and a higher ASA grade are useful for assessing patient conditions and guiding management, they do not determine mortality.

In our study, the APACHE II score was significantly higher in non survivors [Table/Fig-2]. Similarly, other authors have also found the APACHE II score to be a predictor of mortality [3,4,16,21]. Although the SOFA score was high in non survivors, it was not significantly associated with M&M. Other studies, however, found a significant difference in the SOFA score between survivors and non survivors [3-5,16]. The overall SOFA score was low in our study, which could explain the non-significant difference. Although the Mannheim Peritonitis Index (MPI) was not found to be a useful tool for predicting mortality, higher morbidity (CD grades ≥ 3) was associated with a higher MPI in the present study. In contrast, MPI was found to be a useful predictor of mortality in another study, where the association between high CD grade and MPI was not assessed [4].

Different authors have found that anaemia, low Total Leukocyte Count (TLC) (<4000/mm³), and hypoalbuminemia were useful tests for predicting M&M, but we did not find such associations [Table/Fig-2] [3,5,18]. Very few patients had a TLC <4000/mm³ (only 5 patients) in our study. Additionally, severe anaemia (haemoglobin ≤8 g/dL) was not present in any patient. Serum creatinine levels were significantly higher in non survivors and in patients with major complications in our study [Table/Fig-2]. Similarly, in another study, the authors found higher serum creatinine values in non survivors [15]. As septicaemia progresses, it may lead to circulatory collapse, AKI and multiorgan failure, requiring vasopressors and Mechanical Ventilation (MV) support. Although we did not find any difference in preoperative AKI between survivors and non survivors, the difference was significant postoperatively. Higher postoperative vasopressor use and MV support, requiring ICU admission, were observed in the non-survivor group and in patients with major complications [Table/Fig-3]. A similar trend of higher postoperative AKI, vasopressor support, and the need for MV was seen in non survivors in another study [4].

The strengths of the study include: this being a prospective study, a standardised resuscitation protocol was followed using balanced salt solutions. Serial monitoring of lactate was conducted until 24 hours postoperatively to observe the trend. All patients were followed until discharge or mortality, and the final outcome was graded using the Clavien-Dindo (CD) grade. Factors associated with higher CD grades (≥3) were also assessed.

Limitation(s)

This is a single-centre study with a limited number and type of patients. However, the sample size was larger than the statistical calculation based on previous study results. Dynamic indexes of fluid responsiveness were not utilised during resuscitation. Patients with a higher ASA grade (>3), those older than 65 years, and patients with severe chronic diseases were not included in the study, so the results cannot be generalised to all patients.

CONCLUSION(S)

The incidence of M&M is quite high in cases of perforation peritonitis. Non malignant aetiology is more common in developing countries like ours. Among all predictors, lactate levels at 24 hours postoperatively ($Lac_{24\ h\ postop}$) were found to be the best predictor and reliably predicted the chances of mortality at a cut-off of ≥3.2 mmol/L, with an AUROC of 0.786 and an accuracy of 88%. It also predicted morbidity at a level of ≥1.5 mmol/L, with an AUROC of 0.785 and an accuracy of 72%. Therefore, $Lac_{24\ h\ postop}$ may be useful in risk stratification and optimising treatment accordingly. Thus, the authors recommend monitoring the trend of lactate levels for atleast 24 hours postoperatively in patients with perforation peritonitis to identify those at high-risk of morbidity and mortality.

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