



## Role of Lactic Acidosis on Cytokines in Peritoneal Fluid after Damage Control Laparotomy for Trauma

**Short title:** Lactate, peritoneal cytokines in trauma

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*Citation: Dhanushka Vitharana, Jenna Dennis, Sophia Trinh, Paige Deville, Abdul-Razak Masoud, et al. (2025) Role of Lactic Acidosis on Cytokines in Peritoneal Fluid after Damage Control Laparotomy for Trauma. J. of Bio Adv Sci Research, 1(3):1-9. WMJ/JBASR-135*

### Abstract

**Introduction:** In trauma, lactic acidosis has been associated with a robust inflammatory response and poorer outcomes. However, its effect on peritoneal fluid cytokine production following trauma has not been elucidated. The aim of this study was to investigate how lactic acidosis is associated with cytokine production in peritoneal fluid of trauma patients after damage control laparotomy (DCL).

**Methods:** Peritoneal fluid was collected from adult patients undergoing DCL at a Level 1 Trauma Center for blunt or penetrating trauma. Peritoneal fluid cytokine levels were measured using a 10-analyte multiplex assay. Patients were separated by admission serum lactate level: low ( $\leq 2.5$  mmol/L), medium ( $>2.5$  mmol/L and  $\leq 4$  mmol/L) and high ( $>4$  mmol/L) based on previous literature. Univariate and multivariate analyses were used to compare the groups.

**Results:** Of the 61 samples studied from 35 patients, no significant differences in baseline demographics were observed amongst groups. IL-4 significantly differed based on admission lactate and was lowest in the medium group ( $p=0.005$ ). Multivariable analysis however revealed no significant differences in IL-4 levels amongst groups. Levels of other cytokines studied were not significantly different ( $p>0.05$ ). No significant differences in general or postoperative complications were seen with differing lactate levels. There were no significant differences in mortality amongst groups ( $p>0.05$ ).

**Conclusion:** Lactic acidosis in trauma patients is associated with altered peritoneal fluid cytokine levels, specifically IL-4, an anti-inflammatory cytokine that counteracts the pro-inflammatory cascade. Further investigation into the role of lactate as an inflammatory modulator in trauma may provide insight into the local

*inflammatory response to trauma.*

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**Submitted:** 29.11.2025

**Accepted:** 05.11.2025

**Published:** 15.12.2025

**Keywords:** Trauma, peritoneal fluid, cytokine, damage control laparotomy, IL-4

## Abbreviations

**IL – Interleukin**

**DCL – Damage control laparotomy**

**BMI – Body mass index**

**MOI – Mechanism of injury**

**ISS – Injury severity score**

**LOS – Length of stay**

**ICU – Intensive Care Unit**

**DWI – Deep wound infection**

**SWI – Superficial wound infection**

**MSOF – Multisystem organ failure**

**RRT – Renal replacement therapy**

**ARDS – Acute Respiratory Distress Syndrome**

**IQR – Interquartile range**

## Introduction

Traumatic injuries cause significant morbidity and mortality, even beyond discharge [1]. Immediately following trauma, the body produces a pro-inflammatory response by releasing Interferon-gamma (IFN- $\gamma$ ), Interleukin-1 (IL-1), Interleukin-2 (IL-2), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), Interleukin-6 (IL-6), and Interleukin-12 (IL-12) [2]. Peritoneal fluid has been implicated in the pro-inflammatory response after abdominal surgery, leading to the recruitment of leukocytes by cytokine and chemokine production [3]. Cytokines such as TNF- $\alpha$ , IL-6, and IL-10 have been detected in the peritoneal fluid in higher concentrations compared to systemic levels in patients undergoing abdominal surgery [4,5]. After damage control laparotomy (DCL), they have been associated with non-survivorship [4,5]. Moreover, TNF- $\alpha$  and IL-6 levels in the peritoneal fluid have been associated with anastomotic leaks in colorectal patients [6].

Lactic acid, a byproduct of glycolysis, can produce pro- and anti-inflammatory effects. It promotes inflammation by inducing Interleukin-17 (IL-17) production

in lymphocytes [7]. In mouse mast cells, lactate can have an anti-inflammatory effect [7]. Serum lactate can be a marker of illness severity in septic shock. Increasing severity of lactic acidosis on admission and the inability to clear it within 24 hours increases the risk of infection and in-hospital mortality [8-12]. Moreover, in blunt trauma, elevated lactate is significantly associated with increased injury severity, and increased levels of several pro-inflammatory cytokines such as IL-6 and IL-17 can occur severely injured patients compared to mildly- and moderately-injured patients [13].

While lactic acidosis in the setting of trauma has been extensively studied, its association with alterations in peritoneal fluid cytokine levels remain poorly understood. Given that the cytokine profile of peritoneal fluid could better reflect the local inflammatory response to trauma, studying its composition could provide important insights into the inflammatory cascade initiated by traumatic injury. The aim of this study was to investigate whether the severity of lactic acidosis correlated with alterations in the peritoneal fluid cytokine profile in peritoneal fluid of trauma patients undergoing damage control laparotomy (DCL). It was hypothesized that peritoneal fluid cytokine levels differed in patients based on the severity of lactic acidosis on admission.

## Materials and Methods

### Subject Population

A prospective study was conducted at a Level 1 Trauma Center from November 2022 to August 2024 after obtaining approval from the local Institutional Review Board (New Orleans, LA). Adult patients who underwent DCL following blunt or penetrating trauma were included. Informed consent was obtained from patients or their legally authorized representatives prior to obtaining peritoneal fluid samples. Patients were

separated into three groups by their admission lactate levels: low (lactate  $\leq 2.5$  mmol/L), medium ( $>2.5$  mmol/L and  $\leq 4$  mmol/L) and high ( $>4$  mmol/L) based on previous literature [10]. Patients excluded from the study were those who were under the age of 18 years, belonged to vulnerable patient populations including pregnant people and prisoners, or those who underwent DCL for non-traumatic injuries.

### Study Methods and Data Collection

Baseline demographic information including age, gender, race, body mass index (BMI), mechanism of injury (MOI), injury severity score (ISS), blood alcohol level on admission, smoking history and presence of shock on admission were collected.

Secondary outcomes included clinical outcomes, postoperative complications, as well as general in-hospital complications. The clinical outcomes studied included hospital length of stay (LOS), Intensive Care Unit (ICU) LOS and mortality. Postoperative complications included anastomotic leaks, enterocutaneous fistulae, necrotizing soft tissue infections, fascial dehiscence, enterotomies, intra-abdominal abscesses (deep wound infections, DWIs), superficial wound infections (SWIs) and hematomas. General complications included multisystem organ failure (MSOF), acute renal failure requiring renal replacement therapy (RRT), and acute respiratory failure or acute respiratory distress syndrome (ARDS).

### Cytokine Analysis

Peritoneal fluid was collected from patients at the time of the initial operation or during subsequent takeback operations. Cytokines in the peritoneal fluid sample were identified and levels were quantified using a Millipore™ 10-analyte Milliplex map cytokine magnetic bead panel analysis kit according to the manufacturer's recommendations (pg/mL). All samples were run in triplicates. The cytokines analyzed included IFN- $\gamma$ , IL-4, IL-6, IL-1 $\beta$ , IL-8, IL-17A, IL-10, FGF-2, MCP-1, VEGF. These cytokines were selected based on their roles in both the local peritoneal and systemic inflammatory responses. The primary outcome was cytokine levels in the peritoneal fluid. Cytokine levels were compared amongst the three groups.

### Statistical Analysis

Data were analyzed using the SAS/STAT software, version 9.4 of the SAS System for PC (SAS Institute Inc., Cary, NC, USA). Categorical variables were compared amongst the three groups using the Exact test for variables with cell counts less than five or the Chi-Square test for variables with cell counts of five or more, and continuous variables were compared using Wilcoxon rank-sum test. When a significant difference was observed in median cytokine levels amongst the groups in the univariable analysis, a multivariable analysis was conducted on the log-transformed values, adjusting for age, sex, ISS, MOI, and presence of shock on admission. Continuous variables were presented as the median (interquartile range, IQR). Statistical significance was defined as  $p < 0.05$ .

## Results

### Baseline Demographics

Overall, 61 samples were studied from 35 patients. No significant differences in baseline demographics were observed. ( $p>0.05$ ). (Table 1).

**Table 1:** Patients' demographic and clinical characteristics (n=35).

Item	Low (n=6)	Medium (n=9)	High (n=20)	p-value <sup>1</sup>
Age (days), median (IQR)	53.5 (31, 59)	33.0 (32,45)	29.5 (23,28.5)	0.252
BMI (kg/m <sup>2</sup> ), median (IQR)	26.4 (20.8,32.1)	25.1 (23.2,30.2)	27.0 (24.2,33.1)	0.422
ISS, median (IQR)	21 (13,34)	22 (18,29)	28 (19,34)	0.641
Male, % (n)	83.3 (5)	66.7 (6)	90.0 (18)	0.304
Race, % (n)				0.895
African American	66.7 (4)	66.7 (6)	50.0 (10)	
Caucasian	33.3 (2)	22.2 (2)	40.0 (8)	
Other	0 (0)	11.1 (1)	5.0 (1)	
Unknown	0 (0)	0 (0)	5.0 (1)	
Mechanism of Injury, % (n)				0.376
Blunt	16.7 (1)	22.2 (2)	45.0 (9)	
Penetrating	83.3 (5)	77.8 (7)	55.0 (11)	
Smoking status, % (n)				0.615
Never	33.3 (2)	55.6 (5)	30.0 (6)	
Current	50.0 (3)	22.2 (2)	20.0 (4)	
Former	0 (0)	11.1 (1)	15.0 (3)	
Unknown	16.7 (1)	11.1 (1)	35.0 (7)	
Alcohol at admission, % (n)	0 (0)	33.3 (3)	35.0 (7)	0.231

<sup>1</sup>Categorical variables were compared using the Exact test for variables with cell counts less than five or the Chi-Square test for variables with cell counts of five or more, and continuous variables were compared using Wilcoxon rank-sum test.

BMI = body mass index, IQR = interquartile range.

### Peritoneal Fluid Cytokine Analysis

Of the cytokines studied, IL-4 levels were significantly different amongst the groups ( $p=0.025$ ). Notably, while overall decreased IL-4 levels were seen with increased admission lactate, levels in the medium group were the lowest (low: 6.8 [0.2,15.8], medium: 0.1 [0.01,0.1], high: 17.1 [0.5, 123]). (Table 2).

**Table 2:** Cytokine Levels in the Peritoneal Fluid Based on Admission Lactate Levels

Cytokine	Low (n=6)	Medium (n=9)	High (n=20)	p-value <sup>1</sup>
IFN- $\gamma$	0.5 (0,2.6)	3.6 (1.1,3.9)	0.9 (0.1,3.1)	0.16
IL-1- $\beta$	344 (17.3,3089)	150 (16.8,469.4)	103 (15,836)	0.825
IL-4	6.8 (0.2,15.8)	0.1 (0.01,0.1)	17.7 (0.5,123)	0.025
IL-6	5170 (4147,8672)	7713 (1237,11954)	5072 (3500,9422)	0.888
IL-8	9168 (500,10684)	6655 (1291,9742)	6172 (4520,8429)	0.393
IL-10	1007 (746,1117)	271 (150,401)	325 (123,709)	0.229
IL-17A	0.1 (0,4)	4.5 (1.7,5.4)	1.4 (0.1,5.2)	0.114
FGF-2	1214 (729,1335)	2039 (1651,3346)	1383 (766,2098)	0.348
MCP-1	5714 (5646,9680)	5115 (4062,8216)	5660 (5416,7631)	0.542
VEGF	80.3 (54.2,361)	264 (166,295)	217 (150,530)	0.652

<sup>1</sup>Categorical variables were compared using the Exact test for variables with cell counts less than five or the Chi-Square test for variables with cell counts of five or more, and continuous variables were compared using Wilcoxon rank-sum test. Values presented as median (IQR).

IQR = interquartile range.

While peritoneal fluid levels of the other cytokines measured were not statistically significant ( $p>0.05$ ), distinct trends were observed amongst the groups. Levels of IFN- $\gamma$ , IL-6, IL-17A, FGF-2 and VEGF increased from the low to medium groups, however decreased in the high group. The cytokines IL-1 $\beta$ , IL-8 and IL-10 had overall decrease in cytokine levels with increasing lactic acid severity, however the differences amongst groups did not reach statistical significance ( $p>0.05$ ). (Table 2).

A multivariable analysis for IL-4 levels was then performed to adjust for the effect of age, sex, ISS, MOI and presence of shock on admission. After controlling for these variables, no significant differences in IL-4 levels were observed amongst the groups ( $p>0.05$ ).

### Clinical Outcomes

Of the clinical outcomes studied, no significant were observed amongst groups ( $p>0.05$ ). Mortality was highest in the high lactate level group, however this difference was not statistically significant ( $p=0.074$ ). (Table 3).

### General and Postoperative Complications

No significant differences in post-operative complication rates were observed amongst the groups ( $p>0.05$ ). (Table 3).

**Table 3:** In-Hospital Outcomes of Peritoneal Fluid Samples. (n=35)

Outcome	Low (n=6)	Medium (n=9)	High (n=20)	p-value <sup>1</sup>
Hospital LOS (days), median (IQR)	12 (5, 31)	24 (8,36)	25.5 (11,43)	0.599
ICU LOS (days), median (IQR)	4 (2,21)	5 (3,13)	9 (3,26.5)	0.695
Any complication post-op, % (n)	50.0 (3)	44.4 (4)	45.0 (9)	1
Mortality, % (n)	16.7 (1)	0 (0)	30.0 (6)	0.215
MSOF, % (n)	16.7 (1)	0 (0)	40.0 (8)	0.065
RRT, % (n)	16.7 (1)	11.1 (1)	25.0 (5)	0.844
UTI, % (n)	0 (0)	0 (0)	10.0 (2)	1
Sepsis bacteremia, % (n)	16.7 (1)	33.3 (3)	10.0 (2)	0.336
SWI, % (n)	0 (0)	22.2 (2)	0 (0)	0.086
DWI, % (n)	33.3 (2)	22.2 (2)	45.0 (9)	0.574
Resp failure/ARDS/ALI, % (n)	0 (0)	33.3 (3)	30.0 (6)	0.331
PNA, % (n)	0 (0)	22.2 (2)	10.0 (2)	0.608

<sup>1</sup>Categorical variables were compared using the Exact test for variables with cell counts less than five or the Chi-Square test for variables with cell counts of five or more, and continuous variables were compared using Wilcoxon rank-sum test.

ICU = Intensive Care Unit, IQR = interquartile range, LOS = length of stay.

### Discussion

Lactic acidosis and traumatic injuries independently have been implicated in triggering systemic cytokine release to create a profound inflammatory response in affected patients. The role of lactic acidosis on peritoneal fluid cytokine levels following trauma is not well understood. This study aimed to investigate the association between lactic acidosis and cytokine concentrations in the peritoneal fluid cytokine levels of trauma patients undergoing damage control laparotomy for trauma. The results from this study suggest that lactic acidosis in the setting of trauma is associated with decreased IL-4 in the peritoneal fluid, thus could provide a glimpse into the local inflammatory response following insult.

Following trauma, the early response to injury is characterized by a predominance of pro-inflammatory mediators followed by a period of immunosuppression [14]. IL-4 is an anti-inflammatory cytokine secreted by Th2 T-cells that can influence tissue adhesion and inflammation, as well as downregulate the production of several pro-inflammatory cytokines [15,16]. Increased serum IL-4 levels have been associated with increased injury severity [17]. Burn patients who developed abdominal compartment syndrome, and were non-survivors, were found to have higher levels of IFN- $\gamma$ , IL-4, IL-6 and IL-10 in the peritoneal fluid compared to survivors [18]. However, in orthopedic trauma, lower IL-4 levels were seen in the injured group compared to healthy controls [19].

In our study, we found that decreased peritoneal fluid IL-4 levels were associated with increasing admission serum lactate levels, with the most pronounced change occurring in the medium lactate level group. No clear interactions between serum lactate levels and serum or peritoneal fluid IL-4 levels have been established in previous literature. A possible explanation for the findings of our study is that lactate contributes to the downregulation of anti-inflammatory cytokine production, such as Interleukin-4 (IL-4). Lactate accumulation leads to lactylation of M1-macrophages and inhibition of IL-4 and IL-17 production in Natural Killer T-cells [20]. Yet it would be expected, with inhibition of anti-inflammatory pathways, there would be a subsequent increase in pro-inflammatory cytokines with increasing lactate levels, which was not observed in our study. In fact, pro-inflammatory cytokines such as IFN- $\gamma$  and IL-6 were not significantly different amongst the groups, which have previously been found to be elevated after traumatic injury or in the setting of abdominal surgery [4,18].

Moreover, when controlling for several baseline demographics and the presence of shock on admission, no differences in IL-4 levels were noted amongst the groups. The lack of elevation in pro-inflammatory cytokines observed in our study, as well as IL-4 levels no longer being significant after our sub-analysis, suggests underlying mechanisms could be influencing the expression of both pro-and anti-inflammatory cytokines, which would warrant further study.

In addition, our study showed that changes in peritoneal fluid cytokine levels were not consistent with increasing severity. Interestingly, the medium group consistently had cytokine levels in contrast to those of the high group, reaching either a peak or a trough. This could suggest that at differing serum concentrations, lactate could be associated with either upregulation or downregulation of peritoneal fluid cytokine levels. Study of lactate in vitro has shown that lactate and its acidified form, lactic acid, may have different effects on CD8<sup>+</sup> T-cell motility as well as CD4<sup>+</sup> T-cell migration [21]. However it is unclear from existing literature whether lactate exhibits differing inflammatory responses based on the concentration. Further investigation is required to discern how lactate concentration could modulate the interaction of

peritoneal cytokines and the overall balance between pro- and anti-inflammatory responses to trauma.

No significant differences in clinical outcomes or rates of postoperative complications were observed with differing lactate levels. From the results of this study, it is unclear whether differences in IL-4 levels amongst groups could be associated with the differences in clinical outcomes, as this is most likely multifactorial.

Interestingly, there was no significant difference in mortality between the groups. Serum lactate in the emergency department has been implicated in injury severity, multi-organ failure, mortality, respiratory complications, increased transfusion requirements and need for emergency operation [22,23]. Furthermore, elevated peritoneal fluid lactate has been associated with an increased risk of reintervention – by surgical and nonsurgical means – in patients undergoing abdominal surgery [24]. Given that lactic acidosis may portend poorer outcomes in the setting of trauma, it was expected that differences in mortality between the two groups would be present.

### Limitations and Future Directions

There are several limitations to this study that warrant discussion. This is a single-center study with a small sample size which could influence, in part, the lack of significant differences in most of the cytokines studied, as well as the clinical outcomes amongst groups. Furthermore, the samples were not separated based on the time of collection (initial compared to subsequent take back operation) and thus temporal trends in the cytokine expression in the peritoneal fluid. Following a traumatic stimulus, the early response to injury is characterized by a predominance of pro-inflammatory mediators followed by a period of immunosuppression [14]. It is plausible that variations in cytokine levels between the three groups may become evident when examined over time.

Moreover, in the peritoneal fluid samples collected, it was not possible to fractionate the peritoneal fluid from other bodily fluids such as blood that may be present in the sample. As a result, the cytokine profile demonstrated in our study may in part reflect the systemic inflammatory response as well as the local response. Given the paucity of literature on the peritoneal fluid

cytokine profile following trauma, it is difficult to determine how this local peritoneal fluid response differs from the systemic response.

In the study, the effect of specific cytokines expressed in the peritoneal fluid on clinical outcomes, as well as survivorship, amongst the groups was not studied. Death following trauma has been associated with increased IL-4, IL-6, IL-8, TNF- $\alpha$  [25]. Further investigations into potential associations between cytokines and clinical outcomes may enable specific cytokines to be used as biomarkers of disease and as potential therapeutic targets.

### Conclusion

This study represents one of the first investigations into the correlation between lactate and the immunologic response in peritoneal fluid, as measured by cytokine levels, following trauma. In the peritoneal fluid, lactic acidosis could be associated with an impaired anti-inflammatory response to trauma through suppression of IL-4. This study provides insights into the local inflammatory response to trauma and may help us to understand how it contributes to the overall systemic response. Ultimately these findings may help improve the understanding of the immune response to trauma and may be an area of interest for the development of treatments to improve outcomes for trauma patients.

### Study Type

Not applicable

### Supplementary Materials

Not applicable.

### Author Contributions

DV and AS were the main researchers for this study and writers of this manuscript. JD and JH were responsible for the technical work. DV, JD, ST, PD, CR, JH, PG, JD and JR were involved in sample collection. CL performed the statistical analysis of the data. AS and JD planned the study, wrote the protocol and were involved with data analysis.

### Acknowledgements

Disclosures: Alison Smith, MD, PhD is member of Prytime Medical Advisory Board and consultant for Aroa Biosurgery.

**Funding:** None.

### Meeting Presentation

Vitharana, D, Dennis, J, Trinh, S, Deville P, Rais F, Ramos C, Robinson J, Duchesne J, Greiffenstein P, Smith AA. Role of Lactic Acidosis on Cytokines in Peritoneal Fluid After Damage Control Laparotomy for Trauma. Academic Surgical Congress Annual Meeting. QuickShot Oral Presentation. February 2025.

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