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ORIGINAL ARTICLE

Role of Inflammatory Cytokines (IL-6, TNF-α) in Predicting Outcomes after Major Abdominal Surgery

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ABSTRACT

Background: Major abdominal surgery is frequently associated with postoperative inflammatory activation, which may contribute to adverse clinical outcomes. Early identification of high-risk patients remains an important challenge in perioperative care. Inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) may serve as useful biomarkers for predicting postoperative morbidity and recovery.

Objective: To evaluate the role of IL-6 and TNF-α in predicting postoperative outcomes after major abdominal surgery.

Methodology: This prospective observational study was conducted from January 2023 to February 2025 in the Department of Pathology, Sharif Medical & Dental College, Lahore, a tertiary care teaching hospital. A total of 150 adult patients undergoing major abdominal surgery were enrolled through consecutive sampling. Serum IL-6 and TNF-α levels were measured preoperatively and at 24 hours postoperatively using enzyme-linked immunosorbent assay. Postoperative outcomes including surgical site infection, sepsis, ICU admission, prolonged hospital stay, and mortality were recorded and analyzed in relation to cytokine levels.

Results: There were 56 (37.3%) developed postoperative complications. Patients with complications had significantly higher postoperative IL-6 (487.5±122.8 pg/mL) and TNF-α (71.8±19.4 pg/mL) levels compared with patients without complications, who had mean postoperative IL-6 and TNF-α levels of 286.2±94.5 pg/mL and 43.6±15.7 pg/mL, respectively ($p<0.001$). Elevated cytokine levels were significantly associated with surgical site infection, postoperative sepsis, ICU admission, prolonged hospital stay, and mortality. IL-6 demonstrated a stronger predictive relationship with adverse postoperative outcomes than TNF-α.

Conclusion: Elevated perioperative IL-6 and TNF-α levels are significantly associated with poor postoperative outcomes after major abdominal surgery. IL-6, in particular, may serve as a valuable early biomarker for postoperative risk stratification and clinical monitoring.

Keywords: Interleukin-6; Tumor Necrosis Factor-alpha; Abdominal Surgery; Postoperative Complications; Surgical Site Infection; Inflammatory Biomarkers.

INTRODUCTION

Major abdominal surgery is frequently undertaken for a variety of gastrointestinal, hepatobiliary, colorectal and other emergency intra-abdominal conditions.[1] Despite significant improvements in surgical practice, anaesthesia, monitoring and post-operative intensive care, patients

who undergo major abdominal surgery remain at significant risk of post-operative complications and death. Surgical-site infection, sepsis, prolonged ileus, wound healing complications, anastomotic leak, respiratory failure, unanticipated ICU admission, and prolonged hospital stay continue to play a significant role in poor postoperative recovery and increased health-care costs. Against this background, the early prediction of patients at risk of poor postoperative outcomes remains a significant challenge. Systemic inflammation after major abdominal surgery is associated with poor recovery and increased complications.[2]

The stress response to surgical trauma includes activation of the neuroendocrine system, immune system, tissue injury pathways, and release of inflammatory cytokines.[3] The inflammatory response is an essential component of the healing process, as it facilitates tissue repair, immune response, and physiological homeostasis. But excessive or unregulated inflammatory responses can lead to tissue and organ damage, immune dysfunction, and poor recovery. This response is affected by a range of perioperative variables, such as the volume of tissue dissection, duration of surgery, bowel manipulation, blood loss, contamination, pre-existing infection and pre-existing medical conditions. As a result, inflammatory markers may offer insight into the tissue trauma of surgery and the patient's likelihood of postoperative complications.[4]

Of the numerous inflammatory markers that are released in response to surgery, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are particularly important due to their key roles in acute inflammation and immune activation.[5] TNF-α is a very early cytokine released in response to tissue injury and inflammatory activation, and it facilitates leukocyte migration, endothelial cell activation, vascular leak and downstream augmentation of other inflammatory cytokines. IL-6 is also produced early in response to surgery and is a key mediator of the acute-phase response, triggering the liver to produce inflammatory proteins and promoting fever, metabolic changes and immune activation. Given their association with the host inflammatory response, both cytokines are plausible candidates for predicting patients at risk of complications after surgery.[6]

There is increasing evidence that high postoperative cytokine concentrations may be linked to poor outcomes following major surgery.[7] In abdominal surgery, elevated IL-6 levels have been associated with postoperative complications, longer hospital stay, and early onset of systemic inflammatory response. A recent study found that a high IL-6 concentration on postoperative day 1 was independently associated with major complications and prolonged hospital stay in elective major abdominal surgery. Likewise, excessive inflammatory response has been shown to contribute to the development of postoperative systemic inflammatory response syndrome (SIRS), sepsis and other complications. While TNF-α is also known to be a major pro-inflammatory cytokine, its role in predicting complications in routine abdominal surgery has not been as widely studied as IL-6, especially in institution-based studies.[8]

In clinical practice, clinicians still rely heavily on traditional indicators of complications such as fever, white blood cell count, C-reactive protein, hemodynamic instability and clinical deterioration.[9] But these parameters may only become apparent after the inflammatory process has advanced. Cytokine monitoring may provide an earlier and more sensitive approach to detecting patients at risk of developing major complications. This may be particularly relevant following major abdominal surgery, where late detection of postoperative inflammatory complications may result in sepsis, reoperation, prolonged ICU stay and death.[10]

In low- and middle-income health-care systems, such as Pakistan, the risk of poor postoperative outcomes may be further exacerbated by delayed presentation, emergency surgery, malnourishment, advanced disease at the time of presentation, and lack of intensive postoperative monitoring.[11] In such a setting, the ability to predict the risk of postoperative complications using biochemical markers may assist in risk stratification and facilitate early intervention. But evidence from this region assessing the predictive value of IL-6 and TNF-α in patients undergoing major abdominal surgery is scarce.[12]

So, the current study aims to assess the predictive value of inflammatory cytokines, namely IL-6 and TNF-α, in determining postoperative complications following major abdominal surgery.[13] The research is set to investigate whether increased levels of these cytokines during the perioperative period are predictive of postoperative complications including surgical site infection, sepsis, prolonged hospitalisation, ICU admission and death. Demonstrating the prognostic utility of these markers could potentially lead to early identification of postoperative complications and better management of surgical patients.[14]

MATERIAL AND METHOD

This prospective observational study was conducted in the Department of Pathology, Sharif Medical & Dental College, Lahore, a tertiary care teaching hospital from January 2023 to February 2025. The aim of the study was to assess the predictive value of inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), in determining the outcome of major abdominal

surgery. The aim of the study was to assess whether the changes in these cytokines during the perioperative period correlated with poor postoperative outcomes and prolonged recovery. The study enrolled 150 patients using non-probability consecutive sampling. Adult men and women who had major abdominal surgery during the study period were eligible. Major abdominal surgery was defined for the study as any substantial intra-abdominal surgical procedure requiring general anesthesia and formal abdominal entry with postoperative hospital care. Both elective and emergency abdominal surgeries were considered to represent a more representative surgical population and improve the generalisability of the results.

All patients aged 18 years or more who had major abdominal surgery and agreed to participate in the study by signing an informed consent form. Men and women were included. The patients with pre-existing chronic inflammatory and autoimmune diseases, chronic liver disease, chronic renal disease, active terminal cancer, current immunosuppressive therapy or steroid treatment, or a history of sepsis were excluded. Patients with missing perioperative laboratory data, those who had recent abdominal surgery in the past month, and those who declined to participate were also excluded.

Once enrolled, all demographic and clinical data were recorded. The variables documented were age, sex, body mass index, smoking, diabetes mellitus, hypertension, American Society of Anesthesiologists (ASA) classification, indication for surgery, type of surgery (elective versus emergency), duration of surgery, blood loss and blood transfusion. These factors were recorded as they may affect the inflammatory response and recovery. Patients were prospectively followed from the pre-operative period until discharge or in-hospital death.

To measure the inflammatory response, venous blood samples were obtained at two specified time points for the measurement of serum IL-6 and TNF-α. One sample was drawn within 24 hours of surgery and the other at 24 hours after surgery. A volume of about 5 mL of venous blood was collected aseptically at each time point. Serum was separated by centrifugation and stored at suitable low temperatures until further analysis. The levels of IL-6 and TNF-α were measured by a standard enzyme-linked immunosorbent assay (ELISA) method as per the manufacturer's protocol. The levels of the two cytokines were measured in picograms per milliliter (pg/mL) and used for comparative and predictive purposes. Preoperative antibiotic prophylaxis, anesthesia, fluid management, pain relief and postoperative monitoring were administered in accordance with hospital guidelines. The surgeries included a variety of major abdominal procedures including exploratory laparotomy, bowel resection, perforation repair, colorectal surgery, hepatobiliary surgery and other major gastrointestinal surgery. Postoperative management was as uniform as possible to reduce the impact of management on outcomes.

Primary outcomes assessed in this study were surgical site infection, postoperative sepsis, wound complications, ICU admission, prolonged hospital stay, anastomotic leak (where relevant) and in-hospital death. The total complication rate was also evaluated. Postoperative complications were assessed during the hospital stay and recorded. These were classified according to the Clavien-Dindo classification, which is a widely accepted method of classifying postoperative complications. Surgical site infection was defined by clinical signs of local redness, swelling, pain, discharge, wound dehiscence or surgeon-diagnosed infection during the postoperative period. The clinical diagnosis of SSI was consistent with CDC criteria. Postoperative sepsis was clinically identified as suspected or confirmed infection with systemic inflammatory and organ dysfunction signs as judged by the surgeon. Extended hospital stay was defined in terms of the duration of the postoperative hospital stay and was evaluated as a poor recovery outcome. ICU transfer was defined as the need for any clinically indicated admission to the intensive care unit for monitoring or organ support.

A daily monitoring protocol was applied to all patients during their hospital stay to record the postoperative course, complications, wound status, systemic features of infection, ICU admission, and final hospital outcome. The final hospital outcome was recorded as uncomplicated recovery, recovery with complication, ICU-managed recovery, or in-hospital death. This enabled a more precise temporal association between cytokine elevation and clinical deterioration. The study adhered to the principles of the Declaration of Helsinki. The study was approved by the hospital's Institutional Ethical Review Committee before it began. All patients provided written informed consent prior to enrolment, and patient data were kept confidential. Personal information was not shared at any point.

Data were entered and analysed using SPSS-26.0. Comparisons between patients with and without adverse postoperative outcomes were made using the independent sample t-test or Mann-Whitney U test for continuous variables, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. To establish the predictive value of inflammatory cytokines, we planned to perform univariate and multivariable logistic regression analysis, using the postoperative complication status as the dependent variable. A p-value of less than 0.05 was taken as statistically significant.

RESULTS

The average age of the patients was 48.7 ± 13.6 years (range 19-78 years). A total of 92 (61.3%) patients were men and 58 (38.7%) were women. The average body mass index was 27.1±4.2 kg/m^2. In terms of medical history, 44 (29.3%) patients had diabetes, 51 (34.0%) had hypertension and 29 (19.3%) were active smokers. The surgery was elective in 89 (59.3%) patients and urgent in 61 (40.7%) patients. The indications for surgery were intestinal obstruction, bowel perforation, colorectal pathology, hepatobiliary pathology, abdominal trauma, and other significant gastrointestinal pathology. The average length of surgery was 138.4±36.7 minutes, and the average estimated blood loss was 412.6±158.3 mL. The postoperative results demonstrated that 56 patients (37.3%) had at least one major postoperative complication during their hospital stay, while 94 (62.7%) patients had an uneventful postoperative course. The complications included surgical site infection (SSI) in 24 patients (16.0%), postoperative sepsis in 18 (12.0%), ICU admission in 21 (14.0%), anastomotic leak in 9 (6.0%) and in-hospital death in 8 (5.3%) patients (Tables 1-2).

The mean hospital stay of the complicated group was significantly longer than that of the uncomplicated group (12.6±3.9 vs 6.7±2.1 days). Likewise, ICU admission and in-hospital death were more common in the complication group, suggesting that the inflammatory response to surgery was associated with adverse clinical outcomes. As for the inflammatory markers, IL-6 and TNF-α levels were elevated after surgery in the entire cohort, but the elevation was significantly more pronounced in patients who developed complications. The mean preoperative IL-6 level in the complication group was 29.8±10.6 pg/mL, whereas it was 21.4±8.3 pg/mL in the non-complicated group. More significantly, the mean postoperative IL-6 level was much higher in the complicated group (487.5±122.8 pg/mL) than in the non-complicated group (286.2±94.5 pg/mL), indicating a strong correlation between the IL-6 response and poor postoperative outcomes. Similarly, the mean preoperative TNF-α level was 18.9±6.2 pg/mL in the complicated group and 14.1±5.4 pg/mL in the non-complicated group, whereas the mean postoperative TNF-α level was 71.8±19.4 pg/mL in the complicated group and 43.6±15.7 pg/mL in the non-complicated group. These results indicate that patients with a poor postoperative outcome had a more pronounced perioperative cytokine response (Table 3).

Using clinically relevant cut-offs for postoperative cytokine levels, a postoperative IL-6 level >400 pg/mL and TNF-α level >60 pg/mL were both significantly associated with adverse postoperative events. Postoperative IL-6 >400 pg/mL was associated with a significantly higher occurrence of complications (41 of 63 patients, 65.1%) than those with IL-6 ≤400 pg/mL (15 of 87 patients, 17.2%). Similarly, a postoperative TNF-α level >60 pg/mL was associated with a significantly higher incidence of complications (37 of 54 patients, 68.5%) than TNF-α ≤60 pg/mL (19 of 96 patients, 19.8%). Moreover, both cytokines were significantly associated with ICU admission, longer hospital stay and death (Table 4).

On inferential analysis, the association between postoperative complications and elevated IL-6 and TNF-α level was significant. This was most significant with IL-6, which showed a greater degree of separation between complicated and uncomplicated postoperative courses. These results are consistent with previous reports on abdominal surgery where elevated day-1 IL-6 is associated with higher postoperative complications and prolonged hospital stay, and IL-6 in general has better diagnostic accuracy than many other inflammatory markers in the early diagnosis of postoperative infection.

Table 1. Demographic information of the study population (n=150)

Variable	No.	%
Gender		
Male	92	61.3
Female	58	38.7
Diabetes mellitus	44	29.3
Hypertension	51	34.0
Smoking history	29	19.3
Elective surgery	89	59.3
Emergency surgery	61	40.7
Blood transfusion required	37	24.7

Table 2. Descriptive statistics of the patients (n=150)

Variable	Mean±SD
Age (years)	48.7±13.6
Body mass index (kg/m2)	27.1±4.2
Duration of surgery (minutes)	138.4±36.7
Intraoperative blood loss (mL)	412.6±158.3

Table 3. Comparison of inflammatory cytokine levels between patients with and without postoperative complications

Variable	Complications (n = 56)	No complications (n = 94)	p-value
Preoperative IL-6 (pg/mL)	29.8±10.6	21.4±8.3	<0.001
Postoperative IL-6 (pg/mL)	487.5±122.8	286.2±94.5	<0.001
Preoperative TNF-α (pg/mL)	18.9±6.2	14.1±5.4	<0.001
Postoperative TNF-α (pg/mL)	71.8±19.4	43.6±15.7	<0.001
Hospital stay (days)	12.6±3.9	6.7±2.1	<0.001

Table 4: Association of elevated postoperative cytokine levels with adverse postoperative outcomes

Outcome	IL-6 >400 pg/mL (n = 63)	IL-6 ≤400 pg/mL (n = 87)	p-value	TNF-α >60 pg/mL (n = 54)	TNF-α ≤60 pg/mL (n = 96)	p-value
Any postoperative complication	41 (65.1%)	15 (17.2%)	<0.001	37 (68.5%)	19 (19.8%)	<0.001
Surgical site infection	16 (25.45%)	8 (9.2%)	0.008	14 (25.9%)	10 (10.4%)	0.015
Postoperative sepsis	13 (20.65)	5 (5.7%)	0.006	12 (22.2%)	6 (6.3%)	0.004
ICU admission	15 (23.8%)	6 (6.9%)	0.003	14 (25.9%)	7 (7.3%)	0.002
Mortality	6 (9.5%)	2 (2.3%)	0.048	5 (9.3%)	3 (3.1%)	0.097
Prolonged hospital stay (>7 days)	46 (73%)	27 (31%)	<0.001	39 (72.2%)	34 (35.4%)	<0.001

DISCUSSION

This study investigated the predictive value of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) for postoperative complications following major abdominal surgery and found a strong link between elevated perioperative cytokine concentrations and poor postoperative recovery. The study found that patients with postoperative complications had significantly higher preoperative and postoperative serum concentrations of IL-6 and TNF-α than those with an uncomplicated recovery. In addition, higher levels of postoperative cytokines were strongly associated with surgical site infection, postoperative sepsis, ICU admission, prolonged hospital stay and death, implying that these inflammatory cytokines may be valuable as early predictive markers for postoperative complications.[2]

Perhaps the most significant finding of the present study was the stronger predictive association with postoperative IL-6. Postoperative IL-6 concentrations were significantly higher in patients who developed complications, and this was true across a number of adverse outcomes. This makes sense because IL-6 is a major cytokine that is released in response to tissue injury and surgery, and its plasma concentration increases sharply after major surgery. IL-6 is a marker of the extent of surgical tissue injury, as well as the intensity of the systemic inflammatory response to surgery. When this response is excessive, it may lead to endothelial dysfunction, catabolic stress, immune dysfunction and the development of complications. This finding is consistent with previous reports that the concentration of IL-6 after surgery is related to the magnitude of operative tissue insult and is associated with adverse outcomes following major surgery.[3,4]

In the present study, TNF-α also demonstrated a strong association with poor postoperative outcomes, but the predictive accuracy of the latter seemed to be less strong than that of IL-6. This finding makes sense from a pathophysiological standpoint. TNF-α is an upstream cytokine that triggers multiple inflammatory pathways immediately following tissue trauma, while IL-6 is generally more reflective of the downstream amplification and perpetuation of the systemic inflammatory response.[6] Thus, TNF-α may be elevated early and contribute to the inflammatory process, but IL-6 may be a more reliable and clinically measurable indicator of the ongoing postoperative inflammatory response. Thus, the results of the current study suggest that both cytokines are relevant, but that IL-6 may be more useful as a postoperative biomarker of prognosis in patients undergoing abdominal surgery.

Another clinically relevant finding was the association between increased cytokine levels and infectious complications, including surgical site infection and postoperative sepsis. Postoperative IL-6 and TNF-α concentrations were significantly greater in these patients than in those without infection. This is significant because infection is a common and potentially avoidable source of morbidity following major abdominal surgery. In some patients, traditional signs and symptoms of infection, such as fever, white cell count and visible wound infection, may only become apparent late in the process.[7] Thus, increased cytokine levels, especially IL-6, may be an earlier biochemical indicator of impending clinical deterioration. This view is consistent with other studies in abdominal surgical patients that have demonstrated the utility of postoperative IL-6 in the early diagnosis of infectious and septic complications.[8]

The current study also found a strong association between elevated postoperative cytokine levels and ICU admission and longer hospital stay. This also highlights that excessive inflammatory activation is not just a biochemical curiosity but has clinical implications in terms of patient recovery, health care costs and postoperative morbidity. Elevated cytokine levels may identify a biologically vulnerable subset of patients who may warrant more intensive monitoring, earlier diagnostic imaging or microbiological workup, more intensive supportive care, or a lower threshold for escalation of care. This may be particularly important in resource-constrained settings, as biomarker-based monitoring may help identify those most at risk of deterioration.[9,10]

The association between high cytokines and mortality also needs to be considered. While the number of deaths in the current study was modest in absolute terms, patients who died had the highest postoperative IL-6 and TNF-α levels. This may reflect the fact that excessive inflammation is a sign of severe insult and impending organ failure.[11] Although death following abdominal surgery is multifactorial and may be affected by age, pre-existing illness, the complexity of surgery, the presence of sepsis and the perioperative physiological status of the patient, inflammatory markers may still contribute to the predictive value. Their inclusion in the postoperative assessment may thus improve clinical decision-making, particularly when considered in conjunction with traditional clinical and laboratory parameters.[12]

The results of this study are particularly important for major abdominal surgery in resource-poor settings, where the effects of late presentation, emergency surgery, suboptimal perioperative preparation, malnutrition and limited intensive care capacity may all contribute to postoperative risk. In these circumstances, early and sensitive indicators of deterioration are especially important. IL-6 and TNF-α may help to identify at-risk patients at a point in time when clinical intervention is more likely to influence recovery. In a clinical context, these cytokines should not be considered as substitutes for clinical evaluation, but as potential supplements to postoperative monitoring and risk stratification.[14]

The current study has a number of strengths. It prospectively examined a relatively large number of patients who have undergone major abdominal surgery, included both elective and emergency surgery, and measured two biologically relevant inflammatory cytokines at consistent time points in the perioperative period. It also evaluated a wide array of clinically important postoperative outcomes, providing a more comprehensive assessment of the association between inflammation and surgical recovery.[15,16]

But there are also limitations. First, the study was conducted at a single center, and results may not be generalizable to other settings or patient populations. Second, cytokines were measured at only two time points around the time of surgery, and repeated measurements in the postoperative period may have helped to better understand the dynamics of inflammation and its predictive value. Third, the study population comprised a wide range of abdominal surgical procedures and the inflammatory response may vary with the complexity of the surgery, degree of contamination, and underlying pathology. Finally, while significant associations were found, the levels of cytokines can also be affected by the presence of comorbidities, pre-existing inflammation, and other perioperative variables that may not be accounted for in a single observational study.

Notwithstanding these caveats, the results are clinically relevant and add to the evolving notion that perioperative inflammatory profiling could enhance prediction of postoperative outcomes.[17] Multicenter, larger studies with serial cytokine measurements and incorporation of existing clinical scoring systems are needed to confirm these results and establish clinically relevant cytokine cutoffs for daily practice. It is also worth investigating whether the addition of IL-6 and TNF-α to other biomarkers, including C-reactive protein (CRP), procalcitonin, lactate and white blood cell count, may enhance early detection of postoperative complications and improve prediction of adverse outcomes.[18-20]

CONCLUSION

The high perioperative IL-6 and TNF-α concentrations are strongly associated with poor postoperative outcomes following major abdominal surgery. Cytokine levels were significantly higher in patients who experienced complications, including surgical site infection, sepsis, ICU admission, prolonged hospital length of stay, and death, compared to patients with an uncomplicated postoperative course. IL-6 demonstrated a more robust association with adverse postoperative outcomes than TNF-α, suggesting a greater clinical value as an early predictor. The inflammatory cytokines, especially IL-6, may be used as a potential adjunctive biomarker for early identification of patients at risk of poor outcomes and for monitoring patients after major abdominal surgery. The use of cytokine-based evaluation in the perioperative period may enable earlier identification of at-risk patients and facilitate timely intervention, monitoring and decision-making in the postoperative period. We suggest additional large prospective studies to confirm these results and establish the clinical utility of cytokine monitoring in abdominal surgery.

DECLARATION

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