Original Article

Postoperative cytokine levels and their predictive value in critical patients after major abdominal surgery: a retrospective cohort study

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Background: It remains uncertain as to what impact cytokine expression level has on patient outcomes. The association of serum levels of interleukin-1β (IL-1β), IL-2, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), and procalcitonin with critically ill patient outcomes after major abdominal surgery still need to be explored.

Methods: From January 1, 2018 to June 30, 2019, a retrospective cohort study was conducted on patients admitted to the surgical intensive care unit (SICU). Levels of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin were assessed in 1,228 patients undergoing major abdominal surgery with blood samples drawn within 24 h after surgery.

Results: Of the 1,228 patients admitted to the SICU for the first time, 1,152 survived and 76 patients died, with a mortality rate of 6.2% (76/1,228). The results of univariate and multivariate analyses revealed that non-survivors had higher levels of IL-1β (OR =2.438, P<0.001) and IL-2 (OR =1.561, P=0.006). Of 62 (5.0%) readmitted to the SICU, the data of 59 were collected, and showed 46 patients survived and 13 died, giving a mortality rate of 22.0% (13/59), which was 3.5 times higher than the mortality rate during the first SICU admission. Serum IL-6 level associated with SICU readmission (OR =1.37, P=0.029). Furthermore, non-survivors had a longer SICU stay and higher rates of mechanical ventilation and continuous renal replacement therapy (CRRT).

Conclusions: High levels of IL-1β and IL-2 were associated with mortality, and a high level of IL-6 was a risk factor for SICU readmission in critically ill patients who underwent major abdominal surgery. The mortality rate was higher during the second SICU stay.

Keywords: Cytokine level; major abdominal surgery; critically ill patients; mortality; surgical intensive care unit readmission (SICU readmission)

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Introduction

Abdominal surgery is a commonly conducted procedure which, because of progress in surgical and anesthetic techniques and perioperative management, has shown a marked decrease in mortality in recent times. Abdominal surgery carries a 1.5% to 40% mortality rate (1,2). Intraoperative oxygen debt, including reduced systemic oxygen availability and the temporary interruption of blood flow to splanchnic organs, is directly correlated with patient outcomes (3-5). This may be because the surgical procedure and splanchnic ischemia can activate monocytes, macrophages, and endothelial cells, resulting in elevated blood interleukins' levels produced by these cells (6). Cytokine responses are correlated significantly with the magnitude of surgical stress, which reflected by the complexity of operation, duration of the surgery, and the amount of intraoperative blood loss and transfused (7).

An increasing number of studies have investigated whether interleukins are implicated in the pathogenesis of postoperative complications. The serum level of interleukin-6 (IL-6) was associated with outcomes and the severity of organ failure in critically ill patients (8,9) and could be used to predict acute kidney injury (AKI) development. Increased postoperative IL-6 levels were associated with complications, specifically sepsis, reoperation, anastomotic dehiscence, and respiratory insufficiency (10), and elevated IL-6 and IL-8 levels were found in severe trauma patients who developed acute respiratory disease syndrome (ARDS) (11). Perioperative systemic inflammatory response syndrome (SIRS) is characterized by complex alterations in cytokine levels. The balance between TNF-α and IL-10 seemed to determine the occurrence of postoperative complications (7), and the perioperative assessment of C-reactive protein (CRP), IL-6, IL-8, and IL-10 levels helped to predict and monitor postoperative atrial fibrillation (12).

Early identification of developing complications may facilitate clinical decision-making and improve their outcome (10). However, cytokine responses in critically ill patients after major abdominal surgery still under-investigated. And the correlation of cytokine levels and clinical outcomes in these patients have not been described fully.

The aim of this study was to investigate serum cytokine levels in critically ill patients after major abdominal surgery. To this end, IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin were measured to further explore the association between these variables and clinical outcomes, such as mortality and surgical intensive care unit (SICU) readmission. Furthermore, we also evaluated the correlation between cytokine levels and readmission to the SICU. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2171/rc).

Methods

Setting and patients

After the SICU admission, all the patients or their legal guardians provided written informed consent for the standard therapy and nursing care procedure. Prior to the analysis, all patient information was anonymized and deidentified.

This retrospective study was performed in a 50-bed surgery department and 28-bed SICU in a tertiary teaching hospital. Patients included all mechanically ventilated, critically ill patients who underwent emergency or elective major abdominal surgery. Patients were excluded if the data on demographic and clinical characteristics was missing, or information on cytokine levels after SICU admission was absent. A total of 1,228 patients were recruited in this study. All the enrolled patients received standard perioperative anesthetic management and surgery therapy.

Data collection

From January 1, 2018 to June 30, 2019, the following data were extracted: socio-demographic information, admitting diagnosis, type of surgery (emergency or elective), cytokine levels, and organ support therapy [including mechanical ventilation and continuous renal replacement therapy (CRRT)]. All the information was recorded by trained staffs during SICU stay.

The procedures detailed in this study were performed in accordance with the standards of the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee on Human Experimentation of Zhongshan Hospital, Fudan University (No. B2020-107R).

Cytokine measurements

Blood samples were collected to test cytokines' level. Five milliliters of blood was obtained after postoperative venipuncture of a peripheral vein under sterile conditions

within 24 h following the surgery. Blood was collected into sterile tubes, and kept at –80 ℃ after centrifugation. Concentrations of the parameters of interest were measured through an IMMULITE 1000 Immunoassay System (Siemens, Berlin). Normal levels of detection were as follows: IL-1β: lower than 5 pg/mL; IL-2: 223–710 U/mL; IL-6: lower than 3.4 pg/mL; IL-8: lower than 62 pg/mL; IL-10: lower than 9.1 pg/mL; TNF-α: lower than 8.1 pg/mL; procalcitonin: lower than 0.5 ng/mL.

Outcomes

The investigated outcomes included hospital mortality and several SICU-specific outcomes, including readmission rate, length of SICU stay, tracheostomy, receipt and duration of mechanical ventilation therapy, and receipt and duration of renal replacement therapy. Mechanical ventilation therapy included positive pressure ventilation via endotracheal tube or tracheostomy, and renal replacement therapy included all forms of CRRT and intermittent hemodialysis.

Statistical analysis

SPSS Statistics for Windows, Version 22.0 (Chicago, IL) was used for statistical analyses.

Data with nonnormal distributions was presented as medians and interquartile ranges (IQRs), and data with normal distributions was presented as means ± standard deviations (SDs). The missing data was interpolated by average value. Independent sample *t*-test, Mann-Whitney-Wilcoxon test and the Chi-square test were used for between-group comparisons, and descriptive statistics was used for outcome frequency. Multilevel mixed-effects logistic regression analysis was conducted for checking the relationship between cytokine levels and outcomes. The odds ratio (OR) and 95% confidence intervals (CI) were reported. Those variables that showed significance in univariate analysis were also included in multiple logistic regression analysis to examine independent effect. Overall survival curves were plotted by the Kaplan-Meier analysis. A P value <0.05 indicated statistical significance.

Results

Demographic and clinical characteristics

A total of 1,228 patients who presented between January 1, 2018 and June 30, 2019, were included. The overall mortality rate was 6.2% (1,152 patients survived, and 76 died). The mortality rate of patients undergoing emergency surgery was 11.1% (69/621), which was much higher than that of those undergoing elective surgery (1.0%). However, the mortality rate of cancer patients was much lower than that of noncancer patients (2.8% *vs.* 8.7%). Length of SICU stay and mechanical ventilation in the non-surviving group were longer. And the rates of SICU readmission, mechanical ventilation, CRRT therapy, tracheotomy, and emergency surgery were higher. Demographic and clinical characteristics are shown in *Table 1*.

Cytokine levels increased in non-survivors

To investigate the influence of cytokine levels on hospital mortality, we assessed the differences in cytokine levels. The results showed that non-survivors had higher levels of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin (*Table 2*). A significant correlation between serum IL-1β and IL-2 levels and mortality. However, no significant differences were observed in IL-6, IL-8, IL-10, TNF-α, or procalcitonin levels and mortality (*Table 3*).

IL-6 levels increased in patients readmitted to the SICU

Of the 1,228 patients, 62 were readmitted to the SICU, and the readmission rate was 5.0%. The readmitted group patients had higher rates of mechanical ventilation therapy, CRRT therapy, and emergency surgery.

Higher levels of IL-2, IL-6, IL-10, TNF-α, and procalcitonin were found in readmitted patients than in the patients who were not readmitted (*Table 4*). Univariate analyses showed that higher IL-6 concentration was correlated with higher SICU readmission rate. However, no such correlation was found in multivariate analysis (*Table 5*).

Correlation between cytokine levels and outcomes in patients readmitted to the SICU

Among the 62 patients readmitted to the SICU, 59 had their cytokine levels tested during their second stay. Overall, 46 patients survived, and 13 died, giving a mortality rate of 22.0% (13/59), which was much higher than that during the first SICU stay (6.2%). Among the 59 patients readmitted to the SICU, four were admitted a third time, with a rate of third SICU admission of 6.8%. Of these, two patients died, and the mortality rate was 50.0% (2/4).

To explore outcomes and risk factors, we assessed the

Table 1 Baseline patient characteristics (n=1,228)

Variables	Outcome (n=1,228)		$t/z/\chi^2$	P value
	Non-survivors (n=76)	Survivors (n=1,152)		
Age (years)	72.01±15.09	68.79±14.45	1.879	0.061
Sex, No. (%)			0.103	0.748
Male	47 (6.4)	691 (93.6)		
Female	29 (5.9)	461 (94.1)		
Length of SICU stay (h)	339.84±725.67	77.18±147.60	9.664	<0.001
Length of SICU stay, No. (%)			75.394	<0.001
>7 days	27 (25.7)	78 (74.3)		
≤7 days	49 (4.4)	1,074 (95.6)		
SICU readmission, No. (%)			30.218	<0.001
Yes	14 (22.6)	48 (77.4)		
No	62 (5.3)	1,104 (94.7)		
Mechanical ventilation, No. (%)			89.894	<0.001
Yes	68 (14.5)	402 (85.5)		
No	8 (1.1)	750 (98.9)		
Length of mechanical ventilation (h)	437.04±657.49	82.64±179.83	8.893	<0.001
Tracheotomy, No. (%)				
Yes	22 (36.1)	39 (63.9)	98.685	<0.001
No	54 (4.6)	1,113 (95.4)		
CRRT, No. (%)			129.152	<0.001
Yes	27 (37.5)	45 (62.5)		
No	49 (4.2)	1,107 (95.8)		
Length of CRRT therapy (h)	102.24±73.98	89.58±89.68	0.632	0.535
Emergency surgery, No. (%)				
Yes	69 (11.1)	552 (88.9)	57.804	<0.001
No	6 (1.0)	598 (99.0)		
Unknown	1 (33.3)	2 (66.7)		
Cancer, No. (%)			17.883	<0.001
Yes	15 (2.8)	513 (97.2)		
No	61 (8.7)	639 (91.3)		

SICU, surgical intensive care unit; CRRT, continuous renal replacement therapy.

Table 2 Cytokine levels in survivors and non-survivors (n=1,228)

Cytokines	Outcome (n=1,228)		z	P value
	Non-survivors (n=76)	Survivors (n=1,152)		
IL-1β (pg/mL), No. (%)			−7.181	<0.001
≤5	56 (4.9)	1,094 (95.1)		
5–10	8 (16.0)	42 (84.0)		
≥10	12 (42.9)	16 (57.1)		
IL-2 (U/mL), No. (%)			−7.958	<0.001
223–710	9 (1.8)	500 (98.2)		
710–1,000	10 (3.9)	246 (96.1)		
1,000–2,000	25 (7.8)	295 (92.2)		
2,000–3,000	16 (18.6)	70 (81.4)		
≥3,000	16 (28.1)	41 (71.9)		
IL-6 (pg/mL), No. (%)			−4.61	<0.001
<3.4	1 (2.7)	36 (97.3)		
3.4–50	11 (2.9)	366 (97.1)		
50–100	13 (5.4)	227 (94.6)		
100–200	12 (5.7)	200 (94.3)		
≥200	39 (10.8)	323 (89.2)		
IL-8 (pg/mL), No. (%)			−5.934	<0.001
<62	33 (3.8)	844 (96.2)		
62–100	12 (8.3)	132 (91.7)		
100–150	10 (13.9)	62 (86.1)		
150–200	2 (5.3)	36 (94.7)		
≥200	19 (19.6)	78 (80.4)		
IL-10 (pg/mL), No. (%)			−5.292	<0.001
<9.1	27 (3.8)	686 (96.2)		
9.1–20	16 (5.6)	271 (94.4)		
20–50	11 (8.5)	118 (91.5)		
50–100	7 (15.6)	38 (84.4)		
≥100	15 (27.8)	39 (72.2)		
TNF-α (pg/mL), No. (%)			−5.986	<0.001
<8.1	6 (1.6)	364 (98.45)		
8.1–15	20 (4.5)	424 (95.5)		
15–30	20 (7.7)	241 (92.3)		
30–50	17 (13.0)	83 (87.0)		
≥50	13 (24.5)	40 (75.5)		

Table 2 (*continued*)

Table 2 (*continued*)

Cytokines	Outcome (n=1,228)		z	P value
	Non-survivors (n=76)	Survivors (n=1,152)		
Procalcitonin (ng/mL), No. (%)			−4.26	<0.001
<0.5	21 (3.3)	620 (96.7)		
0.5–2	18 (7.9)	211 (92.1)		
2–5	13 (8.6)	138 (91.4)		
5–10	10 (13.0)	67 (87.0)		
≥10	14 (10.8)	116 (89.2)		

IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 3 Analysis of factors associated with patient outcomes

Variables	β	SE	P value	OR	95% CI
Univariate analysis					
Sex	−0.074	0.317	0.816	0.929	(0.499, 1.730)
Length of SICU stay	−0.938	0.344	0.006	0.391	(0.199, 0.767)
SICU readmission	1.069	0.435	0.014	2.911	(1.241, 6.83)
Mechanical ventilation	1.882	0.444	<0.001	6.565	(2.748, 15.683)
CRRT	1.304	0.379	0.001	3.683	(1.752, 7.743)
IL1	0.891	0.208	<0.001	2.438	(1.622, 3.666)
IL2	0.445	0.162	0.006	1.561	(1.137, 2.142)
IL6	−0.027	0.148	0.854	0.973	(0.728, 1.300)
IL8	−0.035	0.133	0.793	0.966	(0.744, 1.253)
IL10	−0.092	0.162	0.567	0.912	(0.664, 1.252)
TNF-α	−0.098	0.176	0.579	0.907	(0.642, 1.281)
Procalcitonin	−0.076	0.111	0.493	0.927	(0.746, 1.151)
Multivariate analysis					
Length of SICU stay	−0.928	0.321	0.004	0.395	(0.211, 0.741)
SICU readmission	1.201	0.391	0.002	3.323	(1.545, 7.149)
Mechanical ventilation	1.781	0.413	<0.001	5.934	(2.640, 13.338)
CRRT	1.203	0.353	0.001	3.329	(1.667, 6.650)
IL1	0.814	0.169	<0.001	2.257	(1.620, 3.144)
IL2	0.294	0.121	0.015	1.342	(1.059, 1.702)

SICU, surgical intensive care unit; CRRT, continuous renal replacement therapy; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 4 Cytokine levels in patients with or without SICU readmission (n=1,228)

Variables	SICU readmission (n=1,228)		t/z/χ^2	P value
	Yes (n=62)	No (n=1,166)		
Age (years)	72.0±12.9	68.8±14.6	1.679	0.093
Sex, No. (%)			0.991	0.320
Male	41 (5.6)	697 (94.4)		
Female	21 (4.3)	469 (95.7)		
Length of SICU stay (h)	112.8±160.5	80.5±136.7	1.783	0.075
Length of SICU stay, No. (%)			2.972	0.085
>7 days	9 (8.6)	96 (91.4)		
≤7 days	53 (4.7)	1,070 (95.3)		
Mechanical ventilation, No. (%)			24.001	<0.001
Yes	42 (8.9)	428 (91.1)		
No	20 (2.6)	738 (97.4)		
Length of mechanical ventilation (h)	116.4±138.8	76.4±139.7	1.339	0.181
CRRT, No. (%)			16.693	<0.001
Yes	11 (15.3)	61 (84.7)		
No	51 (4.4)	1,105 (95.6)		
Length of CRRT therapy (h)	50.7±29.5	83.6±79.3	–0.713	0.479
Emergency surgery, No. (%)				
Yes	39 (6.3)	582 (93.7)	3.895	0.048
No	23 (3.8)	581 (96.2)		
Not known	0 (0)	3 (100.0)	–1.117	0.264
IL-1β (pg/mL), No. (%)				
≤5	56 (4.9)	1,092 (95.1)		
5–10	4 (7.7)	48 (92.3)		
≥10	2 (7.1)	26 (92.9)		
IL-2 (U/mL), No. (%)			–3.603	<0.001
223–710	15 (3.0)	480 (97.0)		
710–1,000	11 (4.1)	259 (95.9)		
1,000–2,000	22 (6.9)	298 (93.1)		
2,000–3,000	5 (5.8)	81 (94.2)		
≥3,000	9 (15.8)	48 (84.2)		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	SICU readmission (n=1,228)		t/z/χ^2	P value
	Yes (n=62)	No (n=1,166)		
IL-6 (pg/mL), No. (%)			–3.300	0.001
<3.4	2 (5.4)	35 (94.6)		
3.4–50	10 (2.7)	367 (97.3)		
50–100	8 (3.3)	232 (96.7)		
100–200	13 (6.1)	199 (93.9)		
≥200	29 (8.0)	333 (92.0)		
IL-8 (pg/mL), No. (%)			–0.635	0.525
<62	43 (4.9)	839 (95.1)		
62–100	7 (4.9)	135 (95.1)		
100–150	2 (2.9)	68 (97.1)		
150–200	1 (2.7)	36 (97.3)		
≥200	9 (9.3)	88 (90.7)		
IL-10 (pg/mL), No. (%)			–2.132	0.033
<9.1	29 (4.0)	689 (96.0)		
9.1–20	17 (6.0)	266 (94.0)		
20–50	6 (4.7)	123 (95.3)		
50–100	3 (6.8)	41 (93.2)		
≥100	7 (13.0)	47 (87.0)		
TNF-α (pg/mL), No. (%)			–2.575	0.010
<8.1	10 (2.6)	368 (97.4)		
8.1–15	20 (4.5)	424 (95.5)		
15–30	17 (6.7)	237 (93.3)		
30–50	10 (10.0)	90 (90.0)		
≥50	5 (9.6)	47 (90.4)		
Procalcitonin (ng/mL), No. (%)			–2.758	0.006
<0.5	24 (3.6)	644 (96.4)		
0.5–2	13 (5.0)	246 (95.0)		
2–5	8 (7.5)	99 (92.5)		
5–10	8 (12.5)	56 (87.5)		
≥10	9 (6.9)	121 (93.1)		

SICU, surgical intensive care unit; CRRT, continuous renal replacement therapy; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 5 Analysis of factors associated with SICU readmission

Variables	β	SE	P value	OR	95% CI
Univariate analysis					
Sex	0.075	0.309	0.809	1.077	(0.588, 1.974)
Length of SICU stay	–0.056	0.444	0.899	0.945	(0.396, 2.255)
Mechanical ventilation	1.075	0.354	0.002	2.930	(1.465, 5.858)
CRRT	1.002	0.457	0.028	2.724	(1.112, 6.669)
IL-1	–0.159	0.34	0.640	0.853	(0.438, 1.662)
IL-2	0.092	0.17	0.589	1.096	(0.786, 1.529)
IL-6	0.315	0.145	0.029	1.37	(1.032, 1.819)
IL-8	–0.125	0.15	0.405	0.883	(0.658, 1.184)
IL-10	–0.075	0.169	0.656	0.927	(0.666, 1.292)
TNF-α	–0.02	0.182	0.914	0.981	(0.686, 1.402)
Procalcitonin	–0.048	0.119	0.684	0.953	(0.755, 1.203)
Multivariate analysis					
Mechanical ventilation	1.012	0.298	0.001	2.75	(1.533, 4.933)
CRRT	0.824	0.376	0.028	2.279	(1.091, 4.762)
IL6	0.208	0.114	0.068	1.231	(0.984, 1.539)

SICU, surgical intensive care unit; CRRT, continuous renal replacement therapy; IL, interleukin; TNF-α, tumor necrosis factor-α.

differences in cytokine levels between survivors and non-survivors. Non-survivors had higher levels of IL-6 than survivors, but no correlation was noted in other cytokines (*Table 6*).

Prognostic values of the cytokines

Totally, 76 of the 1,228 patients in this study died, and the overall survival rate was significantly lower for patients with higher levels of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin (*Figure 1*).

Discussion

This study shows that as the number of SICU admissions increased, mortality also increased (6.2%<22.0%<50.0%). Major surgery leads to the release of pro- and anti-inflammatory cytokines, and patients with higher levels of IL-1β and IL-2 within the first 24 h after operation had an increased mortality rate, while those with a high level of IL-6 had an increased SICU readmission rate.

Surgical trauma can cause increased pro-inflammatory cytokines expression in circulation with associated postoperative morbidity (13). Kvarnström *et al.* reported that during colorectal surgery, there was an inflammatory response with elevated levels of pro-inflammatory cytokines, and in the early postoperative period, the release of pro-inflammatory interleukins (IL-6 and IL-8) and anti-inflammatory interleukins (IL-10) increased (14). In another study, IL-6, CRP, and procalcitonin expression levels were evaluated on the first postoperative day in patients received major gastrointestinal and gynecologic tumor resection. The results also showed that after surgery, the patients who developed sepsis within 5 days had higher levels of IL-6 on the first postoperative day compared to those who did not experience sepsis (15). High levels of this cytokine are considered to be a negative prognostic factor for disease-free intervals and overall survival (16), and our results showed they also correlate positively with SICU readmission rate. Although univariate analyses only showed IL-6 level (OR =1.37, P=0.029) correlated with SICU readmission rate, the rate was higher in patients with high levels of IL-2, IL-6, IL-10, TNF-α, and procalcitonin. These results suggest cytokine levels influence the outcomes

Table 6 Outcomes of patients readmitted to SICU

Variables	Outcome (n=59)		$t/z/\chi^2$	P value
	Non-survivors (n=13)	Survivors (n=46)		
Age (years)	73.7±15.7	71.8±12.5	0.464	0.644
Sex, No. (%)			0.299	0.584
Male	8 (20.0)	32 (80.0)		
Female	5 (26.3)	14 (73.7)		
Length of ICU stay (h)	64.5±80.1	85.0±70.4	–0.887	0.379
Length of ICU stay, No. (%)			0.000	0.988
>7 days	2 (22.2)	7 (77.8)		
≤7 days	11 (22.0)	39 (78.0)		
Third SICU admission, No. (%)			0.022	0.822
Yes	1 (25.0)	3 (75.0)		
No	12 (21.8)	43 (78.2)		
Mechanical ventilation, No. (%)			2.16	0.142
Yes	11 (27.5)	29 (72.5)		
No	2 (10.5)	17 (89.5)		
Length of mechanical ventilation	468.7±316.0	112.9±120.6	4.608	<0.001
CRRT therapy, No. (%)			5.482	0.019
Yes	5 (50.0)	5 (50.0)		
No	8 (16.3)	41 (83.7)		
Length of CRRT therapy	230.0±28.3	50.7±29.5	6.753	0.007
Emergency surgery, No. (%)				
Yes	13 (33.3)	26 (66.7)	8.551	0.003
No	0 (0)	20 (100.0)		
IL-1β (pg/mL), No. (%)				
Normal (≤5)	12 (21.8)	43 (78.2)	–0.21	0.834
5–10	0 (0)	2 (100.0)		
≥10	1 (50.0)	1 (50.0)		
IL-2 (U/mL), No. (%)			–1.802	0.072
Normal [223–710]	2 (13.3)	13 (86.7)		
710–1,000	1 (10.0)	9 (90.0)		
1,000–2,000	5 (23.8)	16 (76.2)		
2,000–3,000	1 (25.0)	3 (75.0)		
≥3,000	4 (44.4)	5 (55.6)		

Table 6 (*continued*)

Table 6 (*continued*)

Variables	Outcome (n=59)		$t/z/\chi^2$	P value
	Non-survivors (n=13)	Survivors (n=46)		
IL-6 (pg/mL), No. (%)			−2.281	0.023
Normal (<3.4)	0 (0)	2 (100.0)		
3.4–50	0 (0)	9 (100.0)		
50–100	1 (12.5)	7 (87.5)		
100–200	3 (23.1)	10 (76.9)		
≥200	9 (33.3)	18 (66.7)		
IL-8 (pg/mL), No. (%)			−0.776	0.438
Normal (<62)	8 (19.5)	33 (80.5)		
62–100	2 (28.6)	5 (71.4)		
100–150	0 (0)	2 (100.0)		
150–200	0 (0)	1 (100.0)		
≥200	3 (37.5)	5 (62.5)		
IL-10 (pg/mL), No. (%)			−1.864	0.062
Normal (<9.1)	4 (14.8)	23 (85.2)		
9.1–20	2 (11.8)	15 (88.2)		
20–50	3 (50.0)	3 (50.0)		
50–100	2 (100.0)	0 (0)		
≥100	2 (28.6)	5 (71.4)		
TNF-α (pg/mL), No. (%)			−0.352	0.725
Normal (<8.1)	2 (18.2)	9 (81.8)		
8.1–15	4 (21.1)	15 (78.9)		
15–30	3 (18.8)	13 (81.2)		
30–50	2 (22.2)	7 (77.8)		
≥50	2 (50.0)	2 (50.0)		
Procalcitonin (ng/mL), No. (%)			−0.143	0.886
Normal (<0.5)	3 (15.0)	17 (85.0)		
0.5–2	5 (29.4)	12 (70.6)		
2–5	1 (12.5)	7 (87.5)		
5–10	2 (33.3)	4 (66.7)		
≥10	2 (25.0)	6 (75.0)		

SICU, surgical intensive care unit; CRRT, continuous renal replacement therapy; IL, interleukin; TNF-α, tumor necrosis factor-α.

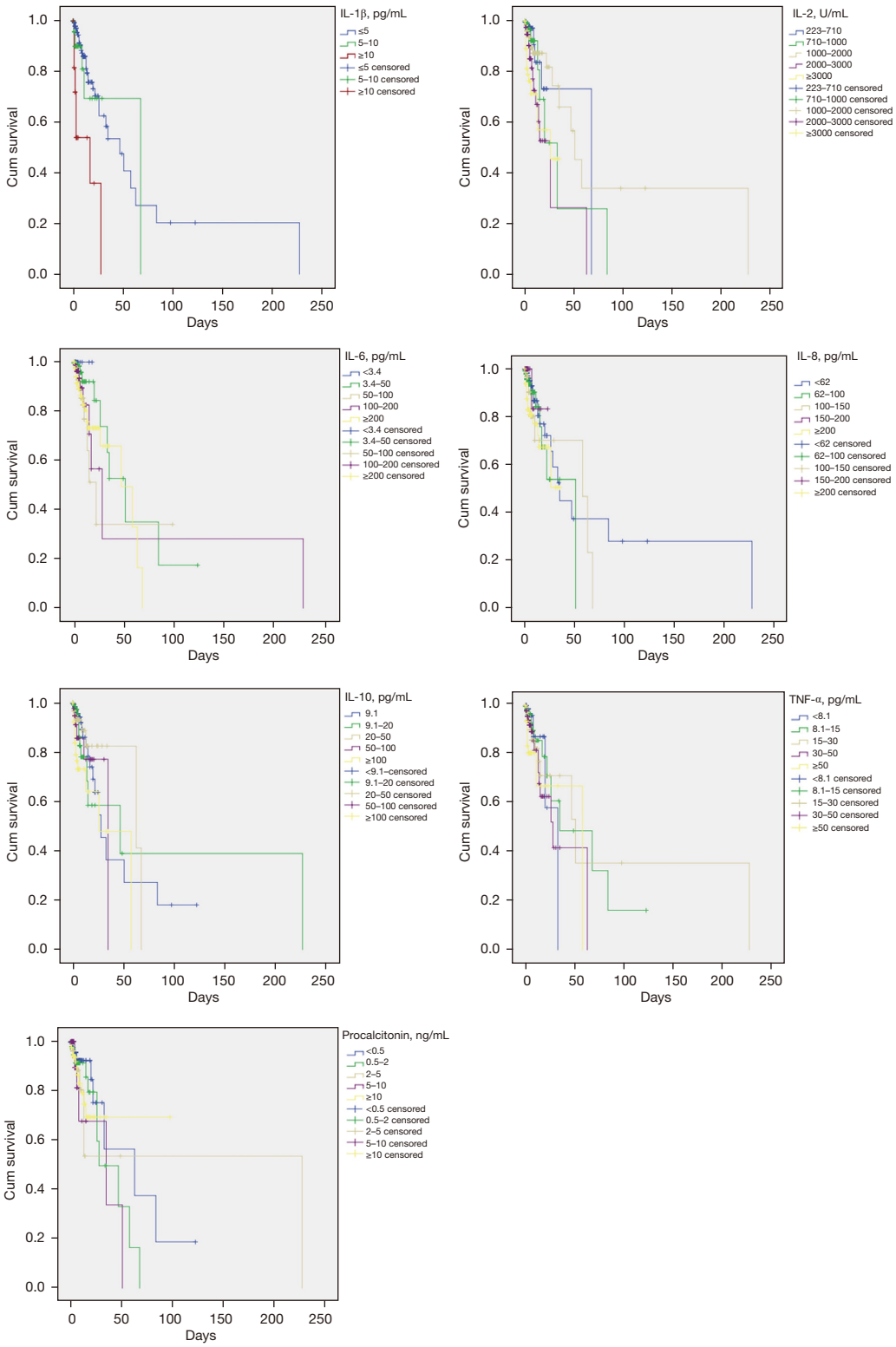

Figure 1 Association between overall survival and IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin levels in 1,228 patients. IL, interleukin; TNF-α, tumor necrosis factor-α.

of critically ill patients undergoing surgery. Further, similar results were noted during the second SICU stay, where the IL-6 level correlated positively with patient outcomes (z=–2.281, P=0.023).

Major abdominal surgery is a common procedure and is associated with a high complication rate, and one method to improve the early detection of complications is to use inflammatory markers. While SIRS pathogenesis may mediated by a variety of pro- and anti-inflammatory mediators (17,18), the mechanism mediating this response is not straightforward (10). In short, tissue damage induces the proliferation of immunocompetent cells, such as monocytes, macrophages, dendritic cells, lymphocytes, and neutrophils (19), which triggers the production of cytokines and chemokines. In this study, higher levels of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and procalcitonin in non-survivors were observed, and univariate and multivariate analyses showed the influence of IL-1β (OR =2.438, P<0.001) and IL-2 (OR =1.561, P=0.006) was significant. These findings are in agreement with those of other researches (20,21). The role of the IL-1 family in the pathogenesis of anti-inflammation has been previously explored (22). IL-1β is a key regulator of the IL-1 family by playing a role in determining inflammation, and is currently being examined in septic patients (23). IL-2 is a key cytokine involved in the immune response, and its regulation can promote the differentiation of T cells and enhance the cytotoxic effect (24). IL-2 was also positively associated with delirium in patients undergoing coronary artery bypass graft surgery (25). From these results, we can infer that IL-1β and IL-2 have distinctive informative value in detecting the state of local immunity in patients after major abdominal surgery. In addition, the anesthesia maintenance technique during surgery may also influence the inflammatory response. Sevoflurane has been demonstrated to suppress the production of IL-6 and IL-8 but not IL-10 and IL-1 receptor antagonists after abdominal surgery (26), while lower plasma levels of both IL-6 and IL-8 were observed after aortic declamping under intravenous anesthesia with propofol, which may promote the production of anti-inflammatory cytokines (27). However, we failed to collect information on the anesthesia technique in this study, and further investigation is required to explore this association.

As shown in *Tables 1* and *4*, length of SICU stay, received emergency surgery, mechanical ventilation and CRRT therapy were associated with mortality. Meanwhile, received emergency surgery, mechanical ventilation and CRRT therapy were also associated with SICU readmission. It is speculated that these factors may correlated positively with disease severity and degree of organ dysfunction. Some previous studies have found that in non-septic patients, cytokines are independent outcome predictors of disease severity scores, including the acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA) scores (28,29).

Conclusions

In conclusion, the mortality rate in patients undergoing major abdominal surgery increased with the number of SICU admissions and cytokine levels. IL-1β and IL-2, were associated with patient outcomes, while the IL-6 level was associated with the SICU readmission rate. In short, IL-1β, IL-2, and IL-6 levels could add value in early clinical decision-making for patients undergoing major abdominal surgery. Further study is required regarding therapeutic interventions targeting cytokine signaling networks to modify inflammatory and autoimmune diseases as well as cancer.

Limitations

The limitations of this study are as follows. First, we detected cytokines only within 24 h after the operation. The time between surgery and the collection of blood samples was somewhat variable among patients due to variations in surgery starting times, and dynamic cytokine levels during the early phase may have influenced the results. Therefore, sequential assessments of cytokine level changes may provide further evidence for the associations. Second, the anesthesia maintenance technique was not analyzed, and this may also influence the inflammatory response during surgery. Third, this was a single-center retrospective study in patients after major abdominal surgery, and multi-center prospective studies are required to verify the results.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2171/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2171/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2171/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The procedures detailed in this study were performed in accordance with the standards of the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee on Human Experimentation of Zhongshan Hospital, Fudan University (No. B2020-107R). All the patients or their legal guardians provided written informed consent for the standard therapy and nursing care procedure.

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