Interleukin-6 and Hospital Length of Stay after Open-heart Surgery

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ABSTRACT

Background: Interleukin-6 (IL-6) is a multi-function, pro-inflammatory cytokine that is chronically elevated in heart diseases. Research suggested that IL-6 may play an important role in the development of systemic inflammatory response syndrome (SIRS) following cardiopulmonary bypass (CPB) used in major open-heart surgery. The present study capitalized on a previous report that used non-laboratory preoperative data of 235 patients undergoing open-heart surgery to predict their length of hospitalization (LOH) following open-heart surgery.

Methods: All patients underwent cardiac surgery (e.g., CABG, valve repair or valve replacement surgery), requiring CPB. Two weeks prior to their scheduled operation, trained research assistants blinded to cardiac indices and laboratory data recruited patients for a psychosocial study and conducted interviews. Key cardiac indices were obtained from a national database: the Society of Thoracic Surgeons' (STS) Adult Cardiac Database at the hospital. Blood samples were collected three days postoperatively for biomarker assays. Plasma was stored within 30 minutes of acquisition. Plasma IL-6 was measured using a sandwich enzyme immunoassay kit, Quantikine High-Sensitivity IL-6 (R&D Systems, Minneapolis MN) with no modification of the manufacturer protocol.

Results: Univariate analysis shows that significantly correlated with LOH were older age, more medical comorbidities, perfusion time and postoperative IL-6. Results from the regression model predicting LOH [F (10, N=215)=8.042, $p<.001$, $R^2=.282$], showed that, among known predictors in the previous report and other STS cardiac indices, only age, perfusion time and postoperative IL-6 were significantly associated with LOH ($p<.01$).

Conclusion: Besides the replication of the previous finding in linking postoperative IL-6 and perfusion time, the study demonstrated the link between postoperative plasma IL-6 and LOH.

Interleukin-6 (IL-6) is a multi-function, pro-inflammatory cytokine that is chronically elevated in both heart disease and certain psychiatric disorders, such as depression, commonly comorbited with heart diseases [1-9]. IL-6 was proposed as a biomarker of cardiac disease severity given its link with myocardial gene expression [10] and its direct association with myocardial injury [11]. Involved in the immune-inflammatory response, cytokines are also molecules crucial to wound repair after surgery. Excess preoperative IL-6 levels, however, may impact the heart directly; higher levels have been linked with immediate postoperative heart dysfunction [12].

Cardiopulmonary bypass (CPB) used in major open-heart surgery can induce a systemic inflammatory response syndrome (SIRS) with organ failure and increased morbidity and mortality [13]. Plasma IL-6 may play an important role in the development of SIRS [14]. Research found that IL-6 level significantly elevated one hour after initiation of CPB and reached its peak at six hours [15]. Surgical trauma, abnormal shear stress, ischemia, reperfusion, and hypothermia can activated the secretion of IL-6 that can remain elevated after surgery [13,16–21]. Elevated IL-6 was also found in the cerebrospinal fluid after coronary artery bypass surgery (CABG), which may predict cognitive decline after cardiac and non-cardiac major surgery [10]. Animal experiments have associated increased cardiomyocyte IL-6 and IL-6 gene expression with cardiac malfunction following trauma-induced hemorrhage [2]. IL-6 receptor antibody blockaded down-regulated IL-6 and improved cardiac functions [22].

To our knowledge, few studies have investigated if postoperative plasma levels of IL-6 influence length of hospitalization (LOH) following open-heart surgery. Accordingly, the present study capitalized on a previous report that used non-laboratory preoperative data of over 400 patients undergoing open-heart surgery to predict their LOH [23]. All participants were interviewed prior to the operation. All procedures required CPB, and standardized surgical and medical data were retrieved from the *Society of Thoracic Surgeons'* (STS) national database. Hierarchical multiple regression found that predictor of shorter LOH were female gender ($p<.001$), older age ($p<.001$), more medical comorbidities ($p<.001$), long perfusion time ($p<.001$), low left ventricular ejection fraction (LVEF; $p<.05$), CABG surgery ($p<.05$), and preoperative sense of reverence in secular contexts ($p<.05$), after controlling for key demographics, STS medical indices, depression, and other psychosocial factors [23].

The present study presents data from a subgroup of these participants who agreed to provide blood samples drawn three days postoperatively [24]. These data permit analysis of IL-6 as a predictor of postoperative length of stay after CPB.

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METHOD

Participants

All patients underwent cardiac surgery (e.g., CABG, aneurysm repair, and valve repair or valve replacement surgery), requiring CPB at the University of Michigan Health Systems (UMHS, Ann Arbor MI, USA). Subject eligibility criteria were: (a) aged 35 years or older; (b) scheduled for admission to the UM Health System for non-emergency, non-transplant cardiac surgery within the subsequent 8 weeks; (c) able to speak and understand the English language; (d) cognitively and physically capable of providing informed consent; and (e) permitted to participate by their surgeons. The majority of the sample was male (58%), Caucasian (92%), and currently married (73%), and the average age was 62+12 – (range, 35–89). Attritional analyses found no demographic differences (age, gender, and race) between 481 (61%) consenters and 204 nonconsenters.

Using a separate consent form to reduce patients' burden, subjects in the subgroup of this analysis offered blood samples three-day postoperatively. Attritional analyses found no significant differences in any major socio-demographics, medical, and psychological variables in the present study between these 236 participants and those whose blood samples were not available [24]. Of the sample, 35.1% had CABG, while 40.2% had mitral valve surgery; two types were overlapping [24]. LOH ranged from 0–95 days (M=7.87; SD=9.06). LVEF ranged from 15% to 87% (M=51.87; SD=13.87). Perfusion time ranged from 0 to 333 minutes (M=130.52; SD=55.18). Medical comorbidities ranged from 0 to 11 (M=2.97; SD=2.33).

Procedures and Measures

Two weeks prior to their scheduled operation, nurses screened the study candidates, and trained research assistants (RAs) blinded to cardiac indices and lab data recruited patients for a psychosocial study and conducted interviews [24]. This personal interview gathered information on patients' socio-demographics, presence of medical comorbidities (fifteen conditions such as diabetes, hypertension, and arthritis), mental health status, and sense of reverence. The latter concept was assessed with a checklist developed by psychologists and a psychiatrist as investigators [24]. The STS database provided the standardized indices of cardiac and surgical information, including the presence (1=YES) or absence (2=No) of CABG and *left main diseases*. Other key indices of cardiac function and disease severity selected are *number of diseased arteries* and an indicator for hemodynamic information-LVEF (the percentage of the blood emptied from the ventricle at the end of the cardiac contraction). A surgical variable used was *Perfusion Time* (the total number of minutes on CPB). Peripheral venous blood samples were collected preoperatively between 8 and 10 a.m. Blood was collected in chilled EDTA vacutainers, and centrifuged. The plasma was separated and stored in aliquots at –80ºC.

Plasma IL-6 Assays

Plasma was stored within 30 minutes of acquisition. Plasma IL-6 was measured using a sandwich enzyme immunoassay kit, *Quantikine High-Sensitivity IL-6* (R&D Systems, Minneapolis MN) with no modification of the manufacturer protocol. All samples were measured in triplicate. Colorimetric optical density (O.D.) data were collected using a microplate reader and captured by *Delta-Soft 3* software (Biometallics, Princeton, NJ). The kit manufacturer states that intra-assay precision varies from 6.9-7.8% Coefficient of Variation (CV; n=20). However, our intra-assay precision was determined using samples in triplicate in our sample analysis. Using standards of known concentration, this range was 8.2–11.6%. Thus, 10% CV was established as the acceptable upper limit of intra-assay variation between triplicate measures; any patient sample above 10% CV was subjected to repeat analysis. The manufacturer states that the mean minimum detectable dose is 0.039 pg/mL Raw O.D. data was transformed to pg/mL by regression analysis of a standard curve run for each assay. The log-transformed linearity of each standard curve was considered acceptable with R>0.98.

Statistical Analysis

Statistical analyses were conducted using SPSS 19. Correlations were performed to determine univariate associations of all variables. After list-wise deletion, 235 patients were included in multiple regression analyses. Given the small sample, regression models only included IL-6 with all significant predictors and two other key cardiac variables (the number of diseased arteries and left-main disease >50%) used in the previous analysis [24]. A trimmed model with only significant or near significant predictors (p<.05) were then performed to eliminate the influence of overparametization. To be conservative, all omnibus tests were two-sided and considered to be statistically significant if p<.01 in the final step. Collinearity statistics were inspected (i.e., variance inflation factors or VIF), using a conservative value of VIF<3.

RESULTS

Table 1 presents bivariate correlations among variables entered into the regression model. Significantly correlated with LOH were older age, more medical comorbidities, perfusion time and postoperative IL-6. Age was also correlated with more diseased arteries, comorbidies, sense of reverence in secular context and IL-6. IL-6 was additionally correlated with more diseased arteries, left-main disease >50%, low LVEF, perfusion time and sense of reverence. LVEF and perfusion time were inversely correlated with each other, while left-main disease >50% was correlated with reverence. More diseased arteries were related positively to left-main disease >50%, low LVEF and reverence and inversely to previous CABG. Previous CABG was also correlated with left-main disease >50%. Female gender was correlated with more medical comorbidities but also with fewer diseased arteries, higher LVEF and reverence.

Table 2 presents results from the regression model predicting LOH [F (10, N=215) =8.042, p<.001, R^2=.282]. Among known predictors in the previous report24 and other STS cardiac indices, only age, perfusion time and postoperative IL-6 were significantly associated with LOH (p<.01). Medical comorbidities were only marginally influential (p<.05) and the previous prediction of reference for LOH was eliminated.

Table 1. **Correlations of Predictors**

	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Gender	.091	**.167**	.090	**–.159**	.066	**.190**	.011	**.252**	**.038**	**.119**
2. Age		**.200**	–.101	**.176**	–.072	–.065	.091	**.154**	**.179**	**.245**
3. Medical Comorbidities			–.068	.062	.014	–.079	.059	.082	.122	**.272**
4. CABG				**–.694**	**.186**	.124	.095	.068	–.065	–.053
5. Number of diseased coronary vessels					**-.399**	**–.187**	–.121	**–.144**	**.145**	.042
6. Left main disease greater than 50%						.129	–.093	**.189**	**–.142**	–.053
7. LVEF							**.180**	.041	**–.205**	–.018
8. Perfusion time in minutes								.053	**.135**	**.332**
9. Reference in secular context									.051	.028
10. Postoperative IL-6										**.315**
11. LOH										

Note. Coefficients with an absolute value greater than or equal to .132 are significant at $p < .05$

The four predictors were then entered into a trimmed model. In this step, however, the age influence vanished but medical comorbidities became a significant predictor (p<.01). The final model [F(4, N=229)=18.72, p<.001, R^2=.250] explained one-quarter of the variance in LOH. As such, patients with poor general health, longer perfusion time during operation and higher levels of postoperative IL-6 had longer hospital stay.

DISCUSSION

Twenty years ago, the concept of SIRS was officially proposed by the American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM), seen as an extension of physiologic self-defense mechanisms [25]. Yet, the protraction of SIRS signifies organ failure and deterioration of the patient status [26,13]. Over the past decade, a number of studies have associated surgical stress with elevated plasma IL-6 following CPB [13-21]. Indeed, plasma L-6 increased with both the duration of SIRS and CPB, indicating its key role in mediating the acute phase response in open-heart surgery patients under CPB [14]. Such a process may cause the potential organ failure due to postoperative microcirculation damage.

Table 2. **Regression Analysis Predicting Length of Hospitalization**

	Step 1	**Step 2 (Trimmed)**
Variable	Beta (SE)	Beta (SE)
Gender	.10 (.07)	
Age	.20 (.00) **	.13 (.00)
Medical Comorbidities	.16 (.02) *	.20 (.02) **
CABG	–.09 (.10)	
# of diseased coronary vessels	–.06 (.04)	
Left main disease > 50%	–.01 (.15)	
LVEF	–.03 (.00)	
Perfusion time in minutes	.34 (.00) ***	.29 (.00) ***
Reference in secular context	–.04 (.03)	
Postoperative IL-6	.17 (.05) **	.21 (.04) ***

*$p < .05$, **$p < .01$, ***$p < .001$

The present study replicated the previous finding in linking postoperative IL-6 and perfusion time [14]. Additionally, we also demonstrated the link between postoperative plasma IL-6 and LOH. The influence of IL-6 is highly significant, even after controlling other predictors (e.g., general health condition and perfusion time) and for key STS cardiac indices. IL-6 has been associated with psychiatric disorders, such as depression [1-9]. Our earlier analysis on this sample, however, did not link preoperative plasma levels of IL-6 and psychological symptoms, when medical factors were controlled [27]. Although the only psychological factor, sense of reverence was found to predict LOH in the earlier report [23], this effect vanished when postoperative IL-6 is used as a predictor in the current analysis. Further, preoperative levels of IL-6 were found to predict psychiatric symptoms one-month after operation [28]. The extent to which these factors interplay in the joint effect on LOH is waiting for further investigation. Due to a small sample, postoperative factors were not examined in this analysis. Finally, age and IL-6 are correlated, while the initial impact of age also diminished in the trimmed model. The fact may suggest the potential mediation of IL-6 in age-LOH, when the overparametization influence is adjusted.

The present study is limited to a single-site convenience sample, relatively small sample size though it is relatively large for testing one biological marker. A non-experimental research design will not permit causality and not eliminate impacts from unmeasured confounders. We did not have plasma IL-6 for the whole sample, though attrition analysis shows no differences between subsamples with or without IL-6. Notwithstanding the shortfalls, the study presents a novel association between IL-6 and hospitalization in open-heart surgery patients.

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