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ORIGINAL RESEARCH

Trauma Preconditioning of Cytokine Response: Comparison of Perioperative Cytokine Profiles in Elective Cardiac versus Orthopaedic Trauma Surgery Patients

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Background: Acute kidney injury (AKI) is a sudden decline in kidney function that poses a significant risk to patients undergoing surgery. Those who develop AKI face higher morbidity and mortality rates, extended hospital stays, and an increased risk of progressing to chronic kidney disease. Previously, we recruited two distinct patient cohorts, one undergoing elective cardiac surgery and one undergoing orthopaedic fracture surgery, to investigate biomarkers involved in the pathophysiology of AKI. This study is a retrospective analysis of data from the two surgical cohorts to examine if there are any similarities between cytokine responses.

Methods: Pre- and post-operative blood and urine biomarker data from elective cardiac surgery patients (n=401) and orthopaedic fracture surgery patients (n=237) were analysed to compare baseline, ratio, and delta change differences.

Results: Pre-operatively, baseline levels of most biomarkers were significantly higher in orthopaedic fracture patients compared to elective cardiac surgery patients. Post-operatively, most biomarker levels remained significantly higher in orthopaedic fracture surgery patients with the exception of urinary anti-inflammatory biomarkers which were higher in cardiac patients. Pre-operatively, renally favourable biomarker ratios were significantly higher in orthopaedic fracture surgery patients compared to elective cardiac surgery patients. In contrast, post-operatively, renally favourable biomarker ratios were significantly higher in elective cardiac surgery patients. The delta differences between pre- and post-operative biomarker levels were generally higher in the elective cardiac surgery patients compared with orthopaedic fracture surgery patients.

Discussion: In this study, in patients which have experienced a fracture, the trauma of the initial injury activated their pro- and anti-inflammatory cytokine responses such that renally favourable ratios prevailed pre-operatively. The further pro-inflammatory response from fracture repair (during surgery) was compensated for by an already established anti-inflammatory perioperative response, suggesting that post-operative compensatory anti-inflammatory responses do not need to be of the same magnitude compared to a non-preconditioned (eg, elective cardiac) response. Cytokine profiling perioperatively could inform clinical decision making and improve patient outcomes by reducing the likelihood of an AKI event.

Keywords: acute kidney injury, biomarkers, cytokines, elective cardiac surgery, orthopaedic surgery

Introduction

Acute kidney injury (AKI) is a major complication of surgery which results in poorer patient outcomes, increased hospital stay and can lead to the development or progression of chronic kidney disease (CKD).[1] In a recent observational study, 18.4% of patients developed AKI following surgery, with urological and cardiac surgery causing the highest rates of AKI (27.6% and 25.9% of patients, respectively).[2]

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There are various risk factors associated with the development of post-operative AKI including demographic risk factors such as age, gender and ethnicity in addition to operation-related risk factors such as intra-operative mean arterial pressure (MAP <60 mmHg),[1] cardiopulmonary bypass time and hypoperfusion duration.[3]

We have recently demonstrated that multiple ratios consisting of urinary anti-inflammatory biomarkers divided by biomarkers of pro-inflammation, hypoperfusion and ischemia reperfusion injury (IRI) are lower in patients who developed cardiac surgery-associated acute kidney injury (CS-AKI).[4] A similar pattern occurred in patients who developed post-trauma orthopaedic surgery acute kidney injury (PTOS-AKI).[5] We concluded that in patients undergoing elective cardiac and orthopaedic fracture surgery, the urinary anti-inflammatory response may protect against the renal-injurious effects of proinflammation, hypoperfusion and IRI.[4,5]

We also demonstrated that ratios consisting of blood anti-inflammatory biomarkers divided by blood biomarkers of proinflammation, are higher in patients who developed AKI in both elective cardiac surgery[4] and orthopaedic fracture surgery.[5] A potential explanation for this is that the levels of blood anti-inflammatory biomarkers increase in response to an underlying proinflammatory response. However, because the smaller proinflammatory blood biomarkers, are more readily filterable by the kidney and are more difficult to measure in blood than their larger anti-inflammatory counterparts, there is an increased ratio of blood anti-inflammatory biomarkers divided by blood proinflammatory biomarkers in conditions of an increased underlying proinflammatory response.[4,5]

Although the above parallels are readily apparent between cardiac and orthopaedic fracture surgery, an important difference between elective cardiac surgery and orthopaedic fracture patients is that the latter sustained a traumatic fracture prior to surgery. Such trauma leads to some blood loss and an activation of the coagulation response pre-operatively. Since an activated coagulation response has long been recognised as an important driver of the proinflammatory response,[6,7] the question arises if a pre-operative orthopaedic trauma preconditions pro- and anti-inflammatory responses prior to the orthopaedic fracture surgery.

Study Objectives and Detailed Hypotheses

Accordingly, this present study retrospectively analyses data from prior studies in patients who developed CS-AKI[4,8] and PTOS-AKI.[5,9] We investigated if there are any significant differences between elective cardiac and orthopaedic fracture surgery patients which might point to traumatic preconditioning of pro- and anti-inflammatory biomarkers, and whether or not any such differences align with cytokine profiles earlier identified as beneficial or injurious to renal function.

Primary Hypothesis

We investigated the hypothesis that trauma pre-conditioning in the orthopaedic fracture surgery patients would lead to significantly higher pre-operative pro- and anti-inflammatory biomarker measurements compared with the cardiac surgery patients.

Secondary Hypothesis

Previously, in cardiac[4] and orthopaedic patients,[5] we identified various renally favourable cytokine ratio combinations which were higher in patients who did not develop AKI. Our hypothesis was that these favourable cytokine ratios (Ratios R1-R4) would be higher pre-operatively in orthopaedic fracture surgery patients compared to cardiac surgery patients, due to trauma preconditioning.

R1 $\frac{urine\ anti-inflammatory\ biomarkers}{blood\ proinflammatory\ biomarkers}$

R2 $\frac{urine\ anti-inflammatory\ biomarkers}{blood\ anti-inflammatory\ biomarkers}$

R3 $\frac{urine\ anti-inflammatory\ biomarkers}{blood\ hypoperfusion\ biomarkers}$

R4 $\frac{urine\ anti-inflammatory\ biomarkers}{blood\ biomarkers\ of\ ischaemia\ reperfusion}$

Tertiary Hypothesis

Finally, we hypothesised that trauma pre-conditioning would lead to significantly lower delta differences between pre- and post-operative biomarker levels in orthopaedic fracture surgery patients, than delta differences between pre- and post-operative biomarker levels in cardiac surgery patients.

Methods

Study Details

Information on the cardiac[4,8] and orthopaedic studies[5,9] has been reported previously. Briefly, for the cardiac study, 401 patients scheduled for elective cardiac surgery between May 2012 and August 2013 within the Cardiac Surgical Unit of the Royal Victoria Hospital, Belfast, UK were recruited. The exclusion criteria included patients if they were <18 years old, had pre-operative dialysis-dependent renal failure, or significant kidney disease (based on an estimated filtration rate (eGFR) <40 mL/min/1.73m^2). For the orthopaedic study, 237 patients who were scheduled for open reduction and internal fixation fracture surgery within the Fracture Unit of the Royal Victoria Hospital, Belfast, UK were recruited. Patients were excluded if they were <18 years old, had a history of significant renal disease or had pre-operative or pre-trauma dialysis-dependent renal failure.

Both the Cardiac and Orthopaedic studies complied with the Declaration of Helsinki, were approved by the Office for Research Ethics Committee Northern Ireland (12/NI/0021), the Royal Victoria Hospital Research Office Research Governance Committee, Belfast, Northern Ireland, and written informed consent was obtained from all participating patients.

Patient blood samples were collected pre-operatively and one day post-operatively. Blood samples were centrifuged, and serum and plasma were aliquoted within 30 minutes of blood collection and stored at −80°C.

Pre- and post-operative eGFR were calculated using the Modification of Diet in Renal Disease (MDRD) study equation using serum creatinine and clinical factors which consider age, gender and ethnicity.[10] In both studies, CS-AKI and PTOS-AKI were defined as a 25% decrease from baseline eGFR according to risk, injury, failure, loss, end-stage (RIFLE) criteria[11] occurring at any time throughout the five-day post-operative period. For the orthopaedic study, it was not possible to determine a baseline eGFR, so patients were assumed to have normal renal function with a baseline eGFR of at least 60 mL/min/1.73m^2. Biomarkers were measured as described previously by Randox Clinical Laboratory Services (RCLS, Antrim, UK, ISO17025 accredited).[8,9]

Statistical Analysis

Statistical analyses were completed using R.[12] Biomarker delta differences were calculated in each study by subtracting the post-operative biomarker value from the pre-operative biomarker value. Significant differences between biomarker values, ratios and delta differences between the cardiac and orthopaedic surgery groups were determined using Mann–Whitney *U*-test, with a p value <0.05 considered as significant (Table 1). To correct for multiple testing post-hoc Bonferroni p-values were also considered (0.0015, 0.0012 and 0.0015, respectively for Tables 2–4).

Table 1 Study Participant Clinical Characteristics

Variable	Cardiac			Orthopaedic		
	Non-AKI (n=273)	AKI (n=71)	p value	Non-AKI (n=138)	AKI (n=63)	p value
Characteristics						
Age (years)	65.4 ± 11.6	68.6 ± 10.7	0.020	78.7 ± 10.9	85.5 ± 6.1	<0.001
Gender (male)	192/273 (70.3%)	50/71 (70.4%)	0.988	29/138 (21.0%)	21/63 (33.3%)	0.089
Comorbidities						
Hypertension	35/268 (13.1%)	10/68 (14.7%)	0.722	38/138 (27.5%)	27/63 (42.9%)	0.046
Diabetes	29/268 (10.8%)	16/68 (23.5%)	0.006	11/138 (8.0%)	4/63 (6.3%)	0.907
Intraoperative conditions						
Packed red blood cells	126/266 (47.4%)	41/67 (61.2%)	0.043	6/115 (5.2%)	2/52 (3.8%)	1.000
Fresh frozen plasma	20/266 (7.5%)	7/67 (10.4%)	0.433	0/115 (0.0%)	1/52 (1.9%)	0.683
Platelet bags	25/266 (9.4%)	8/67 (11.9%)	0.534	4/115 (3.5%)	2/52 (3.8%)	1.000

(*Continued*)

Table 1 (Continued).

Variable	Cardiac			Orthopaedic		
	Non-AKI (n=273)	AKI (n=71)	p value	Non-AKI (n=138)	AKI (n=63)	p value
Postoperative conditions						
Packed red blood cells	110/267 (41.2%)	36/67 (53.7%)	0.065	34/115 (29.6%)	16/52 (30.8%)	1.000
Fresh frozen plasma	39/266 (14.7%)	13/67 (19.4%)	0.340	0/115 (0.0%)	1/52 (1.9%)	0.683
Length of admission (days)	11.0 ± 8.0	13.1 ± 7.2	<0.001	9.8 ± 7.9	12.0 ± 8.3	0.020

Table 2 Biomarker Levels That Were Significantly Different in Pre- and Post-Operative Cardiac and Orthopaedic Patients

	Biomarker Type	Biomarker	Cardiac [Mean ± SD]	Orthopaedic [Mean ± SD]	p-value	Change
Pre-operative	Blood anti-inflammatory	sTNFR1 (Serum)	0.487 ± 0.759 (n=324)	0.799 ± 0.345 (n=174)	<0.001	Orthopaedic ↑
	Blood anti-inflammatory	sTNFR2 (Serum)	0.517 ± 0.477 (n=324)	0.987 ± 0.797 (n=174)	<0.001	Orthopaedic ↑
	Blood anti-inflammatory	IL-1Ra (Serum)	122.982 ± 225.601 (n=324)	347.906 ± 413.527 (n=175)	<0.001	Orthopaedic ↑
	Blood anti-inflammatory	IL-10 (Plasma)	1.810 ± 5.862 (n=318)	3.210 ± 7.634 (n=184)	<0.001	Orthopaedic ↑
	Blood hypoperfusion	H-FABP (Serum)	9.403 ± 34.507 (n=322)	14.656 ± 15.555 (n=183)	<0.001	Orthopaedic ↑
	Blood hypoperfusion	VEGF (Plasma)	35.299 ± 23.448 (n=318)	54.612 ± 48.520 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	IL-6 (Plasma)	8.530 ± 41.424 (n=318)	76.471 ± 121.440 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	IL-8 (Plasma)	4.387 ± 5.770 (n=318)	12.780 ± 36.708 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	TNFα (Plasma)	2.731 ± 7.947 (n=318)	4.011 ± 6.090 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	MCP-1 (Plasma)	137.407 ± 50.517 (n=318)	204.594 ± 124.028 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	MIP-1α (Plasma)	6.315 ± 30.653 (n=315)	6.293 ± 6.312 (n=184)	<0.001	Cardiac ↑
	Blood proinflammatory	NGAL (Plasma)	658.558 ± 309.175 (n=319)	909.768 ± 441.739 (n=184)	<0.001	Orthopaedic ↑
	Blood proinflammatory	sIL2Rα (Serum)	0.195 ± 0.223 (n=324)	0.260 ± 0.363 (n=174)	<0.001	Orthopaedic ↑
	Blood proinflammatory	MMP9 (Serum)	18.352 ± 23.015 (n=324)	58.657 ± 56.136 (n=174)	<0.001	Orthopaedic ↑
	Blood IRI	Midkine (Serum)	1153.256 ± 1449.082 (n=269)	2265.953 ± 2144.934 (n=128)	<0.001	Orthopaedic ↑
	Urine IRI	Midkine (Urine)	329.353 ± 651.104 (n=279)	1897.309 ± 2055.507 (n=141)	<0.001	Orthopaedic ↑
	Urine anti-inflammatory	IL-1Ra (Urine)	2570.767 ± 4569.763 (n=310)	4642.025 ± 6637.355 (n=162)	<0.001	Orthopaedic ↑
	Urine anti-inflammatory	sTNFR1 (Urine)	0.781 ± 0.841 (n=322)	3.142 ± 3.048 (n=171)	<0.001	Orthopaedic ↑
	Urine anti-inflammatory	sTNFR2 (Urine)	1.322 ± 1.556 (n=322)	4.579 ± 3.781 (n=170)	<0.001	Orthopaedic ↑
	Urine proinflammatory	NGAL (Urine)	110.474 ± 183.431 (n=310)	324.152 ± 350.299 (n=162)	<0.001	Orthopaedic ↑
	Urine proinflammatory	IL-12p40 (Urine)	7.606 ± 45.919 (n=323)	6.271 ± 10.314 (n=171)	<0.001	Cardiac ↑
	Urine proinflammatory	IP-10 (Urine)	19.217 ± 47.639 (n=323)	50.332 ± 135.946 (n=170)	<0.001	Orthopaedic ↑
	Urine proinflammatory	MMP9 (Urine)	8.264 ± 51.839 (n=322)	18.043 ± 37.955 (n=170)	<0.001	Orthopaedic ↑

(*Continued*)

Table 2 (Continued).

	Biomarker Type	Biomarker	Cardiac [Mean ± SD]	Orthopaedic [Mean ± SD]	p-value	Change
Post-operative	Blood anti-inflammatory	sTNFR1 (Serum)	1.002 ± 2.483 (n=319)	1.077 ± 0.453 (n=147)	<0.001	Orthopaedic ↑
	Blood anti-inflammatory	sTNFR2 (Serum)	0.928 ± 0.589 (n=319)	1.330 ± 0.866 (n=147)	<0.001	Orthopaedic ↑
	Blood anti-inflammatory	IL-10 (Plasma)	5.849 ± 11.031 (n=324)	4.834 ± 17.601 (n=158)	<0.001	Cardiac ↑
	Blood hypoperfusion	VEGF (Plasma)	38.375 ± 20.097 (n=324)	57.621 ± 48.381 (n=158)	<0.001	Orthopaedic ↑
	Blood pro-inflammatory	TNFα (Plasma)	2.901 ± 3.318 (n=324)	5.350 ± 11.981 (n=158)	<0.001	Orthopaedic ↑
	Blood proinflammatory	MMP9 (Serum)	29.786 ± 32.167 (n=319)	66.591 ± 60.579 (n=147)	<0.001	Orthopaedic ↑
	Urine anti-inflammatory	IL-1Ra (Urine)	12717.543 ± 10394.569 (n=311)	7770.878 ± 8448.517 (n=153)	<0.001	Cardiac ↑
	Urine anti-inflammatory	sTNFR1 (Urine)	7.136 ± 3.814 (n=319)	5.785 ± 4.144 (n=158)	<0.001	Cardiac ↑
	Urine anti-inflammatory	sTNFR2 (Urine)	8.265 ± 3.610 (n=320)	6.504 ± 4.017 (n=158)	<0.001	Cardiac ↑
	Urine pro-inflammatory	NGAL (Urine)	250.027 ± 271.004 (n=311)	505.338 ± 316.301 (n=153)	<0.001	Orthopaedic ↑
	Urine pro-inflammatory	IL-12p40 (Urine)	5.852 ± 25.678 (n=321)	8.710 ± 21.617 (n=158)	<0.001	Orthopaedic ↑
	Urine pro-inflammatory	IP-10 (Urine)	37.783 ± 93.855 (n=321)	110.177 ± 190.081 (n=158)	<0.001	Orthopaedic ↑
	Urine pro-inflammatory	sIL2Rα (Urine)	0.073 ± 0.063 (n=320)	0.155 ± 0.317 (n=158)	<0.001	Orthopaedic ↑
	Urine pro-inflammatory	MMP9 (Urine)	4.648 ± 5.222 (n=320)	10.810 ± 21.375 (n=158)	<0.001	Orthopaedic ↑

Notes: Full list of biomarkers measured, including non-significant biomarker levels differences are shown in Supplementary File 1. Statistical significance was determined by Mann–Whitney *U*-test with Bonferroni corrected p value <0.0015 considered as significant. Change arrow indicates whether ratio is higher in cardiac or orthopaedic cohorts.

Abbreviations: EGF, epidermal growth factor; H-FABP, heart-type fatty acid-binding protein; IL-1β, interleukin-1 beta; IL-1Ra, interleukin-1 receptor antagonist; IL-5, interleukin-5; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12p40, interleukin-12 subunit p40; IL-15, interleukin-15; IP-10, interferon gamma-induced protein-10; IRI, ischaemia-reperfusion injury; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α; MMP9, matrix metalloproteinase-9; NGAL, neutrophil gelatinase-associated lipocalin; PDGF-BB, platelet-derived growth factor BB; SD, standard deviation; sIL2Rα, soluble interleukin-2 receptor alpha; sIL6R, soluble interleukin-6 receptor; sTNFR1, soluble tumour necrosis factor receptor 1; sTNFR2, soluble tumour necrosis factor receptor 2; TNFα, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

Results

Demographic information for the patients recruited in both studies has been reported previously[8,9] and is briefly described in Table 1. Sensitivity analysis shows that pre-operative eGFR in the cardiac group was not impacted by diabetic or hypertensive status of the patients, therefore supporting the validity of comparing the cardiac and orthopaedic cohorts.

Differences in Baseline Measurements of Biomarkers Between Cardiac and Orthopaedic Surgery Patients

Pre-operatively, there were significant differences between the biomarker levels in the cardiac and orthopaedic fracture surgery patients (Table 2) (non-significant differences shown in Supplementary File 1). Out of 34 biomarkers measured in both studies, 23/34 (67.6%) were significantly different, with 21 biomarkers significantly higher in orthopaedic fracture patients (Table 2). In contrast, two biomarkers were significantly higher in cardiac patients (Table 2). Post-operatively, out of 34 biomarkers measured in both studies, 14/34 (41.2%) were significantly different (Table 2), with 10 biomarkers significantly higher in orthopaedic fracture patients (Table 2). In contrast, four biomarkers were significantly higher in cardiac patients.

Table 3 Renally Favourable Biomarker Ratios That Were Significantly Different Between Cardiac and Orthopaedic Surgery in All Patients

	Ratio Type	Ratio	Cardiac Ratio [Mean ± SD]	Orthopaedic Ratio [Mean ± SD]	p-value	Change
Pre-operative	$\frac{\text{Urine anti-inflammatory}}{\text{Blood proinflammatory}}$(R1)	sTNFR1 (Urine)/NGAL (Plasma)	0.002 ± 0.008 (n=313)	0.004 ± 0.003 (n=163)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/IL-12p40 (Serum)	0.003 ± 0.008 (n=319)	0.011 ± 0.017 (n=157)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/MIP-1α (Plasma)	0.231 ± 0.24 (n=309)	0.629 ± 0.623 (n=163)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/TNFα (Plasma)	0.359 ± 0.361 (n=312)	1.02 ± 0.905 (n=163)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/MCP-1 (Plasma)	0.007 ± 0.009 (n=312)	0.018 ± 0.016 (n=163)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/IL-6 (Plasma)	0.331 ± 0.381 (n=312)	0.086 ± 0.109 (n=163)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/IP-10 (Serum)	0.007 ± 0.009 (n=319)	0.031 ± 0.035 (n=157)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/IL-8 (Plasma)	0.272 ± 0.299 (n=312)	0.519 ± 0.522 (n=163)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/sIL2Rα (Serum)	6.39 ± 10.4 (n=319)	18.8 ± 22 (n=157)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/NGAL (Plasma)	0.003 ± 0.01 (n=313)	0.005 ± 0.004 (n=162)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/IL-12p40 (Serum)	0.004 ± 0.008 (n=319)	0.016 ± 0.026 (n=156)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/MIP-1α (Plasma)	0.388 ± 0.449 (n=309)	0.895 ± 0.719 (n=162)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/TNFα (Plasma)	0.585 ± 0.648 (n=312)	1.47 ± 1.18 (n=162)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/MCP-1 (Plasma)	0.011 ± 0.014 (n=312)	0.026 ± 0.022 (n=162)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/IL-6 (Plasma)	0.544 ± 0.693 (n=312)	0.132 ± 0.174 (n=162)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/IP-10 (Serum)	0.011 ± 0.014 (n=319)	0.044 ± 0.051 (n=156)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/IL-8 (Plasma)	0.455 ± 0.564 (n=312)	0.75 ± 0.66 (n=162)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/sIL2Rα (Serum)	10.5 ± 16.9 (n=319)	27.4 ± 31.5 (n=156)	<0.001	Orthopaedic ↑
		IL-1Ra (Urine)/IL-12p40 (Serum)	18.9 ± 202 (n=307)	21.5 ± 63.6 (n=147)	<0.001	Orthopaedic ↑
		IL-1Ra (Urine)/IL-6 (Plasma)	1250 ± 2770 (n=301)	136 ± 286 (n=152)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/IP-10 (Serum)	28.4 ± 76.5 (n=307)	50.7 ± 128 (n=147)	<0.001	Orthopaedic ↑
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood anti-inflammatory}}$(R2)	sTNFR1 (Urine)/sTNFR1 (Serum)	2.1 ± 2.35 (n=319)	4.05 ± 3.02 (n=157)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/sTNFR2 (Serum)	2.4 ± 3.52 (n=319)	5.84 ± 10.2 (n=157)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/sTNFR1 (Serum)	3.44 ± 3.81 (n=319)	5.96 ± 4.3 (n=156)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/sTNFR2 (Serum)	3.92 ± 6.38 (n=319)	8.65 ± 14.1 (n=156)	<0.001	Orthopaedic ↑
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood hypoperfusion}}$(R3)	sTNFR1 (Urine)/H-FABP (Serum)	0.154 ± 0.178 (n=316)	0.298 ± 0.274 (n=159)	<0.001	Orthopaedic ↑
		sTNFR1 (Urine)/VEGF (Plasma)	0.027 ± 0.036 (n=312)	0.076 ± 0.088 (n=163)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/H-FABP (Serum)	0.248 ± 0.286 (n=316)	0.437 ± 0.372 (n=158)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/VEGF (Plasma)	0.045 ± 0.063 (n=312)	0.108 ± 0.103 (n=162)	<0.001	Orthopaedic ↑
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood IRI}}$(R4)	sTNFR1 (Urine)/Midkine (Serum)	0.001 ± 0.002 (n=263)	0.003 ± 0.004 (n=114)	<0.001	Orthopaedic ↑
		sTNFR2 (Urine)/Midkine (Serum)	0.002 ± 0.003 (n=263)	0.004 ± 0.006 (n=114)	<0.001	Orthopaedic ↑

(*Continued*)

Table 3 (Continued).

	Ratio Type	Ratio	Cardiac Ratio [Mean ± SD]	Orthopaedic Ratio [Mean ± SD]	p-value	Change
Post-operative	$\frac{\text{Urine anti-inflammatory}}{\text{Blood proinflammatory}}$(R1)	sTNFR1 (Urine)/IL-12p40 (Serum)	0.028 ± 0.023 (n=312)	0.021 ± 0.025 (n=138)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/MIP-1α (Plasma)	1.58 ± 1.27 (n=311)	1.04 ± 0.89 (n=147)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/TNFα (Plasma)	3.03 ± 2.05 (n=315)	1.56 ± 1.14 (n=147)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/MCP-1 (Plasma)	0.036 ± 0.025 (n=315)	0.028 ± 0.022 (n=147)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/IL-6 (Plasma)	0.087 ± 0.234 (n=315)	0.057 ± 0.101 (n=147)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/IP-10 (Serum)	0.1 ± 0.209 (n=312)	0.054 ± 0.055 (n=138)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/sIL2Rα (Serum)	47.8 ± 40.1 (n=312)	30.4 ± 31.4 (n=137)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/IL-12p40 (Serum)	0.032 ± 0.023 (n=313)	0.023 ± 0.025 (n=138)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/MIP-1α (Plasma)	1.88 ± 1.55 (n=312)	1.2 ± 1.01 (n=147)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/TNFα (Plasma)	3.59 ± 2.29 (n=316)	1.76 ± 1.16 (n=147)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/MCP-1 (Plasma)	0.043 ± 0.028 (n=316)	0.033 ± 0.024 (n=147)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/IL-6 (Plasma)	0.102 ± 0.241 (n=316)	0.07 ± 0.155 (n=147)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/IP-10 (Serum)	0.11 ± 0.191 (n=313)	0.06 ± 0.053 (n=138)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/sIL2Rα (Serum)	55.6 ± 46.4 (n=313)	33.9 ± 29.6 (n=137)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/NGAL (Plasma)	12.6 ± 11.4 (n=307)	9.63 ± 11.6 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/IL-12p40 (Serum)	45.5 ± 44 (n=304)	27.1 ± 44.3 (n=132)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/MIP-1α (Plasma)	2750 ± 3360 (n=303)	1420 ± 1640 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/TNFα (Plasma)	5030 ± 4570 (n=307)	2020 ± 2190 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/MCP-1 (Plasma)	60.7 ± 60.4 (n=307)	38.8 ± 44.3 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/IL-6 (Plasma)	157 ± 603 (n=307)	66.1 ± 95.3 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/IP-10 (Serum)	143 ± 245 (n=304)	76.8 ± 112 (n=132)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/IL-8 (Plasma)	1440 ± 1890 (n=307)	952 ± 1120 (n=141)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/sIL2Rα (Serum)	85800 ± 99700 (n=304)	37900 ± 47000 (n=131)	<0.001	Cardiac ↑
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood anti-inflammatory}}$(R2)	sTNFR1 (Urine)/sTNFR1 (Serum)	10.2 ± 6.95 (n=312)	5.56 ± 3.67 (n=137)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/sTNFR2 (Serum)	10.9 ± 12 (n=312)	6.69 ± 10 (n=137)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/sTNFR1 (Serum)	12 ± 7.35 (n=313)	6.5 ± 4.19 (n=137)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/sTNFR2 (Serum)	13.1 ± 15.6 (n=313)	8.3 ± 16.2 (n=137)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/sTNFR1 (Serum)	17900 ± 17100 (n=304)	7960 ± 9530 (n=131)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/sTNFR2 (Serum)	18000 ± 24900 (n=304)	9130 ± 20200 (n=131)	<0.001	Cardiac ↑
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood hypoperfusion}}$(R3)	sTNFR1 (Urine)/H-FABP (Serum)	0.42 ± 0.431 (n=313)	0.263 ± 0.259 (n=143)	<0.001	Cardiac ↑
		sTNFR1 (Urine)/VEGF (Plasma)	0.268 ± 0.394 (n=315)	0.132 ± 0.146 (n=147)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/H-FABP (Serum)	0.5 ± 0.518 (n=314)	0.314 ± 0.304 (n=143)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/VEGF (Plasma)	0.303 ± 0.385 (n=316)	0.144 ± 0.122 (n=147)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/H-FABP (Serum)	715 ± 1020 (n=305)	422 ± 661 (n=138)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/VEGF (Plasma)	484 ± 857 (n=307)	160 ± 195 (n=141)	<0.001	Cardiac ↑

(*Continued*)

Table 3 (Continued).

	Ratio Type	Ratio	Cardiac Ratio [Mean ± SD]	Orthopaedic Ratio [Mean ± SD]	p-value	Change
	$\frac{\text{Urine anti-inflammatory}}{\text{Blood IRI}}$ (R4)	sTNFR1 (Urine)/Midkine (Serum)	0.01 ± 0.012 (n=262)	0.005 ± 0.005 (n=120)	<0.001	Cardiac ↑
		sTNFR2 (Urine)/Midkine (Serum)	0.012 ± 0.016 (n=263)	0.006 ± 0.006 (n=120)	<0.001	Cardiac ↑
		IL-1Ra (Urine)/Midkine (Serum)	15.5 ± 23 (n=256)	7.68 ± 12.2 (n=118)	<0.001	Cardiac ↑

Notes: Full list of biomarkers ratios, including non-significant ratios are shown in Supplementary File 2. Statistical significance was determined by Mann–Whitney *U*-test with a Bonferroni corrected p value <0.0012 considered as significant. Change arrow indicates whether ratio is higher in cardiac or orthopaedic cohorts.

Abbreviations: H-FABP, heart-type fatty acid binding protein; IL-1Ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-8, interleukin-8; IL-12p40, interleukin-12 subunit p40; IP-10, interferon gamma-induced protein-10; IRI, ischaemia-reperfusion injury; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α; NGAL, neutrophil gelatinase-associated lipocalin; SD, standard deviation; sIL2Rα, soluble interleukin-2 receptor alpha; sTNFR1, soluble tumour necrosis factor receptor 1; sTNFR2, soluble tumour necrosis factor receptor 2; TNFα, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

Table 4 Significant Delta (Δ) Differences in Biomarkers Measured Pre- and Post-Operatively Between Cardiac and Orthopaedic Surgery Patients

Biomarker Type	Biomarker	Cardiac Δ Difference [Mean ± SD]	Orthopaedic Δ Difference [Mean ± SD]	p value	Change
Blood anti-inflammatory	sTNFR1 (Serum)	0.516 ± 1.776 (n=316)	0.273 ± 0.352 (n=142)	<0.001	Cardiac ↑
Blood anti-inflammatory	EGF (Plasma)	−8.555 ± 130.156 (n=314)	−2.522 ± 23.706 (n=152)	<0.001	Orthopaedic ↑
Blood anti-inflammatory	IL-1Ra (Serum)	542.734 ± 537.269 (n=316)	259.122 ± 545.411 (n=143)	<0.001	Cardiac ↑
Blood anti-inflammatory	IL-10 (Plasma)	4.162 ± 9.650 (n=314)	1.951 ± 14.523 (n=152)	<0.001	Cardiac ↑
Blood pro-inflammatory	IL-8 (Plasma)	14.256 ± 61.985 (n=314)	4.846 ± 48.934 (n=152)	<0.001	Cardiac ↑
Blood pro-inflammatory	MCP-1 (Plasma)	108.568 ± 155.348 (n=314)	28.947 ± 111.519 (n=152)	<0.001	Cardiac ↑
Blood pro-inflammatory	MIP-1a (Plasma)	−0.347 ± 29.347 (n=310)	0.579 ± 3.088 (n=152)	<0.001	Orthopaedic ↑
Blood pro-inflammatory	NGAL (Plasma)	452.044 ± 420.025 (n=315)	44.540 ± 380.879 (n=152)	<0.001	Cardiac ↑
Blood pro-inflammatory	IL-12p40 (Serum)	−120.941 ± 185.884 (n=316)	−35.119 ± 153.503 (n=143)	<0.001	Orthopaedic ↑
Blood pro-inflammatory	IL-15 (Plasma)	0.180 ± 10.695 (n=310)	0.616 ± 0.594 (n=152)	<0.001	Orthopaedic ↑
Blood pro-inflammatory	sIL6R (Serum)	0.121 ± 0.668 (n=316)	0.041 ± 0.650 (n=142)	<0.001	Cardiac ↑
Blood IRI	Midkine (Serum)	705.269 ± 1665.164 (n=269)	−130.205 ± 1923.366 (n=128)	<0.001	Cardiac ↑
Urine IRI	Midkine (Urine)	2254.982 ± 1619.421 (n=279)	893.048 ± 2067.282 (n=141)	<0.001	Cardiac ↑
Urine anti-inflammatory	IL-1Ra (Urine)	10224.628 ± 11362.783 (n=306)	2889.569 ± 10199.448 (n=143)	<0.001	Cardiac ↑
Urine anti-inflammatory	sTNFR1 (Urine)	6.361 ± 3.830 (n=315)	2.466 ± 3.203 (n=148)	<0.001	Cardiac ↑
Urine anti-inflammatory	sTNFR2 (Urine)	6.931 ± 3.744 (n=316)	1.781 ± 3.455 (n=147)	<0.001	Cardiac ↑
Urine pro-inflammatory	IP-10 (Urine)	18.522 ± 102.550 (n=317)	55.500 ± 223.671 (n=147)	<0.001	Orthopaedic ↑
Urine pro-inflammatory	sIL2Rα (Urine)	−0.006 ± 0.074 (n=316)	0.051 ± 0.313 (n=147)	<0.001	Orthopaedic ↑
Urine pro-inflammatory	MMP9 (Urine)	−3.717 ± 50.996 (n=315)	−8.425 ± 40.275 (n=147)	<0.001	Cardiac ↑

Notes: Full list of biomarkers measured, including non-significant biomarker Δ differences are shown in Supplementary File 3. Delta (Δ) change was calculated as post-operative biomarker value minus pre-operative biomarker for each patient. Statistical significance was determined by Mann–Whitney *U*-test Bonferroni corrected p value <0.0015 considered as significant. Change arrow indicates whether Δ change is higher in cardiac or orthopaedic cohorts.

Abbreviations: EGF, epidermal growth factor; IL-1Ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12p40, interleukin-12 subunit p40; IP-10, interferon gamma-induced protein-10; IRI, ischaemia-reperfusion injury; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α; NGAL, neutrophil gelatinase-associated lipocalin; SD, standard deviation; sIL2Rα, soluble interleukin-2 receptor alpha; sIL6R, soluble interleukin-6 receptor; sTNFR1, soluble tumour necrosis factor receptor 1.

Differences in Renally Favourable Ratios Between Patients Undergoing Cardiac and Orthopaedic Fracture Surgery

There were significant differences in the biomarker ratios previously identified as renally favourable (ratios R1-R4) between patients undergoing cardiac and orthopaedic fracture surgery (Table 3) (non-significant ratios shown in Supplementary File 2). Pre-operatively, 31/42 (73.8%) ratios were significantly different between cardiac and orthopaedic fracture surgery patients and of these, 28/31 (90.3%) were higher in orthopaedic fracture patients. Post-operatively, 38/42 (90.5%) ratios were significantly higher in cardiac surgery patients.

Changes in the Delta Difference in Biomarker Levels Pre- and Post-Operatively Between Cardiac and Orthopaedic Fracture Patients

The calculated delta difference in biomarker levels between the pre- and post-operative samples within the cardiac and orthopaedic fracture surgery groups demonstrated significant between-group differences which were largely due to higher baseline levels in the orthopaedic group (Table 4). We report delta (pre-post operative) changes in 19/34 (55.9%) biomarkers that were significantly different between cardiac and orthopaedic surgery groups. Of the 19 biomarkers, 13/19 (68.4%) biomarkers had significantly greater delta (pre-post operative) changes in the cardiac patients relative to the orthopaedic fracture patients (Table 4).

Discussion

Our primary hypothesis of the pre-operative pro- and anti-inflammatory biomarker levels being significantly higher in blood and urine of orthopaedic fracture patients than cardiac patients was partially confirmed with most biomarkers measured being significantly higher in the orthopaedic fracture patients pre-operatively. Many of these significant differences also persisted post-operatively, with blood pro-and anti-inflammatory biomarkers, and urinary pro-inflammatory biomarkers being higher in orthopaedic trauma surgery than in cardiac surgery patients. However, of note, the urinary anti-inflammatory response was higher post-operatively in the cardiac patients. These findings point to the fracture trauma event potentially preconditioning the orthopaedic patients to having higher than normal baseline levels of pro- and anti-inflammatory biomarkers in their blood and urine compared to the cardiac surgery patients. This preconditioning effect persisted post-operatively, save for the urinary anti-inflammatory response. However, while it may be assumed that the lower biomarker levels pre-operatively in cardiac patients may reflect normal levels of pro- and anti-inflammatory biomarkers, our study does not exclude the possibility of cytokine baseline levels in elective cardiac patients being influenced by medications or underlying pathology.[4,8]

Our secondary hypothesis was also partially confirmed in as far as pre-operatively, biomarker ratios (R1-R4) associated with renal protection, appeared to be significantly higher in orthopaedic patients when compared with cardiac patients. In fact, our hypothesis ran counter to the literature, where it has been reported that aging is associated with a gradually increasing pro-inflammatory load (inflammaging)[13] and the normal physiological compensatory anti-inflammatory mechanisms (anti-inflammaging)[14] become generally less efficient in older patients.[15] This decreasing anti-inflammatory compensating capacity is postulated to contribute to the onset of many age-related diseases.[16,17] Among the confounding factors, pre-operative trauma affected all orthopaedic patients, pointing to pre-operative trauma as a potential contributor to this difference.

Since elevation of these biomarker ratios have been associated with reduced risk of AKI in cardiac[4] and orthopaedic surgery,[5] this may suggest that the pre-operative fracture event in orthopaedic surgery potentially confers a beneficial reno-protective cytokine profile prior to surgery. Interestingly, this trend did not continue post-operatively, with all reno-protective ratios significantly higher in the cardiac cohorts. This may suggest that any reno-favourable preconditioning effect of the trauma is less demonstrable post-operatively than pre-operatively.

Any potential explanation for this must take account of the lower post-operative urinary anti-inflammatory biomarker concentration (ratio numerator) in fracture than cardiac patients in parallel with higher (ratio denominator) post-operative levels in fracture than cardiac patients. In this context, it could be argued that the lower post-operative urinary anti-inflammatory biomarkers in fracture patients, despite the presence of higher post-operative blood anti-inflammatory concentrations may suggest that blood anti-inflammatory biomarkers, which are less readily filtered than their pro-inflammatory counterparts, underwent less filtration (from blood into the urine), in fracture than cardiac surgery. An

explanation for this could be that a greater use of vasopressor infusions in cardiac than orthopaedic surgery to prevent hypotension may have enhanced filtration of blood anti-inflammatory biomarkers into urine in cardiac patients, leading to higher post-operative R1-R4 ratios in cardiac than fracture surgery patients. A fall in MAP peri-operatively, in particular secondary to spinal anaesthesia, could reduce anti-inflammatory biomarker glomerular filtration, in which case the increase in blood anti-inflammatory concentration as earlier reported[8] may not translate into a commensurate increase in urinary anti-inflammatory biomarkers. In further support of this, cardiac, but not fracture patients had advanced Level 3 intensive care afforded to them for their first 24 hours post-operatively, which insured constant invasive haemodynamic monitoring and immediate availability of vasopressor and inotrope administration when needed. In contrast, orthopaedic patients generally have only Level 1 ward level care, without access to invasive haemodynamic monitoring and non-immediate access to vasopressors, if hypotension supervenes.

Our tertiary hypothesis was also partially confirmed with the finding that there were significantly reduced delta differences between the pre- and post-operative biomarker levels in orthopaedic surgery patients when compared to the delta difference between pre- and post-operative biomarker levels in cardiac surgery patients. The lower magnitude of the delta difference in orthopaedic fracture patients between pre-surgery baseline and post-operative biomarker levels reflects a significantly higher baseline level following trauma preconditioning. However, in the case of post-operative urinary anti-inflammatory IL-1Ra, sTNFR1 and sTNFR2, the lower ceiling for these values post-operatively in orthopaedic fracture patients than cardiac patients also contributed to the lower delta change for urinary anti-inflammatory biomarkers in orthopaedic fracture patients. A limitation of the previously published studies was that delta change was not considered for biopredictive utility with respect to AKI.[8,9] However, it could be argued that the smaller delta change in orthopaedic fracture surgery patients suggests a more challenging environment for such biomarkers or ratios thereof to be used in prediction of renal dysfunction. This reflects why some biomarkers predictive of renal dysfunction in cardiac patients lose this utility in orthopaedic fracture patients. Nevertheless, several biomarkers and relevant ratios thereof, retained AKI biopredictive ability in both cardiac and orthopaedic surgical settings.[8,9] This reflects the robustness of the biomarkers across a range of surgical specialties, even where the challenge of trauma preconditioning has occurred.

We have previously suggested that inflammatory-mediated tubular injury can happen through (1) direct tubulo-injurious effects of filtered pro-inflammatory biomarkers as well as indirect collateral pro-inflammatory injury secondary to; (2) hypotension; and (3) IRI.[4,5] This is, at least in part, why elevation of the urinary anti-inflammatory response may protect against all three tubulo-injurious processes. This also explains why elevations of ratio-values of urinary anti-inflammatory biomarkers divided by biomarkers of pro-inflammation, hypotension or IRI could be linked to renal protection.

In orthopaedic fracture surgery, trauma preconditioning may lead to enhanced pre-operative reno-protective cytokine profiles as compared with pre-operative cardiac baseline. However, this is less demonstrable post-operatively.

This study could suggest that pre-operative reno-protective preconditioning is a potential strategy for reno-protection in high-risk major surgery. Indeed, this finding may explain why damage control surgery (DCS) in major trauma has brought about improved clinical outcomes,[18] in that it may be allowing reno-protective cytokine profiles to be established before later elective major trauma corrective surgery is attempted. However, in non-trauma major surgery, future investigation may pursue the utility of non-traumatic cytokine preconditioning through pharmacological intervention.

In orthopaedic trauma patients, the initial fracture pre-operatively activates (preconditions) pro- and anti-inflammatory responses demonstrable in blood and urine leading to levels higher than baseline cardiac surgery values. The trauma event also leads to higher reno-favourable biomarker ratios in baseline orthopaedic trauma patients. The further proinflammatory response arising from the later fracture surgery leads to higher post- operative urinary and blood pro-inflammatory biomarkers than in cardiac surgery patients. However, post-operatively, the blood anti-inflammatory response is higher in fracture patients than cardiac patients, whereas the urinary anti-inflammatory response is higher in cardiac patients. This means that reno-favourable cytokine ratios are higher post-operatively in cardiac than orthopaedic trauma patients. This may superficially suggest that the pre-operative trauma preconditioning effect affording pre-operative renally favourable cytokine profiles in orthopaedic trauma patients is not sustained post-operatively. This could, in part, arise from the higher post-operative blood anti-inflammatory response in the orthopaedic patients not translating into a correspondingly higher urinary anti-inflammatory concentration, possibly due to less effective glomerular filtration post-operatively, arising from less invasive haemodynamic

monitoring post-operatively in orthopaedic patients. There is also the possibility that the post-operative compensatory urinary anti-inflammatory response does not need to be as great as it would otherwise be without a preconditioned response. This study further strengthens the benefits of cytokine profiling perioperatively, which could inform clinical decision making to improve patient outcomes and reduce the likelihood of an AKI event.

Conclusions

In summary, this study has described significant differences in cytokine profiles between patients undergoing elective cardiac surgery and orthopaedic fracture surgery. In particular, cytokine profiles earlier identified as being renally favourable pre- and post-operatively in cardiac and orthopaedic surgery are more evident pre-operatively in orthopaedic trauma surgery than elective cardiac surgery patients. This raises the possibility of the preoperative trauma event having preconditioned cytokines to a renally favourable profile. Further work is needed to determine whether non-traumatic (eg. pharmacological) pre-operative cytokine preconditioning could convey a reno-protective effect which may improve patient outcomes and reduce the likelihood of an AKI event. This also raises the possibility that in post-operative orthopaedic trauma patients, where at ward level a degree of hypotension is identified, timely proactive management for this subgroup may be justified in instituting invasive haemodynamic monitoring and therapeutic measures to maintain renally protective blood pressure.

Limitations of the Study

The limitations of the elective cardiac[4,8] and orthopaedic[5,9] surgery studies have been reported previously. As this study has focused on comparing cytokine profiles across two separate study cohorts, there are additional limitations. Notably, there were significant differences between the two study cohorts, including patient age, and co-morbidities of participants. These differences may be a contributor to the incidence of AKI between the study cohorts and may also impact cytokine profiles. We can rule out clinically known pre-trauma CKD in the orthopaedic cohort however we acknowledge that sub-clinical CKD may have been present pre-trauma in some patients. The time of initial fracture was not available in the orthopaedic study cohort. A further limitation of this study is that cytokine profiles may change considerably during surgery and further sampling points may be needed to explore cytokine dynamics. Moreover, as all analysis was univariate, the findings should be interpreted as hypothesis-generating, warranting confirmation in larger cohorts where robust multivariable methods can be applied.

Data Sharing Statement

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Both studies complied with the Declaration of Helsinki, were approved by the Office for Research Ethics Committee Northern Ireland, the Royal Victoria Hospital Research Office Research Governance Committee and written informed consent was obtained from all participating patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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