Inflammatory biomarkers, such as C-reactive protein (CRP), some interleukins (ILs), and procalcitonin, may be elevated owing to known or latent disease, whereby the severity of disease is positively associated with biomarker levels. Inflammatory biomarkers have been associated with the development of cardiovascular disease and poorer outcomes for noncardiovascular and cardiovascular conditions. The exact biomarkers and magnitude of association between biomarkers and cardiac surgical outcomes, however, have not been well characterised. Inflammation may result from a patient’s preoperative state (eg, comorbidities) or from the cardiac surgical procedure itself. In this issue of the Canadian Journal of Cardiology, Heo et al. present a systematic review and meta-analysis of 29 studies and 29,401 patients who underwent cardiac surgery and had one or more inflammatory biomarkers measured perioperatively. They found that biomarkers, especially CRP, before and right after cardiac surgery were associated with an increased risk of all-cause mortality and major adverse cardiovascular events (MACE). Preoperative CRP was associated with increased risks of all-cause mortality (odds ratio [OR] 1.88, 95% confidence interval [CI] 1.60-2.20; $I^2 = 19$%; 11 studies) and MACE (OR 1.73, 95% CI 1.34-2.24; $I^2 = 0$%; 3 studies). Postoperative CRP levels were infrequently studied but also showed elevated odds of all-cause mortality (day 6: OR 7.4, 95% CI 2.90-18.88, 1 study; day 10: OR 11.8, 95% CI 3.50-39.78, 1 study). Other biomarkers, such as IL-6, IL-10, and fibrinogen, had similar findings but were supported with less available evidence.

**Strengths and Weaknesses**

The meta-analysis sheds more light on the association between inflammation, whether preoperative or postoperative, and cardiac surgical outcomes. The authors followed best practices for meta-analyses, including preregistering the protocol, following the appropriate reporting guidelines, conducting quality appraisal and risk of bias assessment, and using random effects models. As such, the findings are robust, further confirmed by the fact that all included studies were of either high ($n = 17$) or good ($n = 12$) quality. The authors also specifically explored the effects in a coronary artery bypass grafting (CABG) subgroup and found consistent findings. Moreover, largely appropriate inclusion and exclusion criteria, such as the exclusion of patients with infection or infective endocarditis because of higher inflammatory biomarker levels and risk of mortality, improve the external validity of findings.

Despite the many strengths, some aspects deserve discussion. The authors did not exclude off-pump minimally invasive or transcatheter procedures nor perform subgroup analyses for on- vs off-pump procedures. The use of cardiopulmonary bypass introduces a systemic inflammatory response and may, therefore, confound findings. In addition, the authors defined MACE as “any composite including one or more of the outcomes of interest,” despite individual studies using different definitions for the MACE composite. Although this is not uncommon for meta-analyses, this results in the pooled MACE finding to be highly sensitive to the composition of the MACE outcomes of the individual studies, whose rates may vary considerably based on the inclusion or exclusion of relevant outcomes. The classic 3-point MACE composite includes stroke, myocardial infarction, and cardiovascular death, whereas other composites may also (or instead) include all-cause mortality, heart failure, other
cardiovascular events, and cardiovascular hospitalisations. Indeed, some studies included in the analysis did not consider stroke as part of MACE, whereas death was defined as either all-cause, cardiovascular, or unspecified, depending on the study. Furthermore, evidence for the association between postoperative CRP and all-cause mortality could be derived from only a single study with large confidence intervals, limiting the interpretation and generalisability. Finally, the current evidence is largely restricted to CRP, and findings may be overestimated owing to study-level effects.

Findings in Context

Despite the limitations, the findings are largely consistent with those from noncardiac surgical meta-analyses, apart from a vascular surgery meta-analysis that found no association between CRP levels and all-cause mortality. In colorectal cancer surgery, increased postoperative CRP levels are associated with poorer overall, cancer-specific, and recurrence-free survival. After stroke, patients with elevated concentrations of IL-6 and CRP are at higher risk of MACE and recurrent stroke even after adjusting for risk factors and management. Finally, across cardiac and noncardiac surgical procedures, higher preoperative levels of inflammatory biomarkers are associated with postoperative delirium, further supporting the association with postoperative complications.

Gaps in Knowledge and Future Research

The study adds an important piece to the cardiac surgical risk stratification puzzle, but other pieces remain missing. The study could inherently not establish causation and only provides information about potential association that may be confounded by known but unadjusted and unknown confounders. Cardiac surgery is an inflammatory event in itself, which may confound findings, and the authors did not exclude off-pump procedures, resulting in procedures with differential inflammatory impact. Distinguishing the effects of procedural inflammation from patients’ preoperative inflammation on cardiac surgical outcomes may further inform optimal patient selection and procedural choice. Furthermore, anti-inflammatory biomarkers are known to also be elevated after cardiac surgery, calling into question whether increases in biomarkers alone are sufficient. Instead, absolute or relative increases or concurrently moderate increases of anti-inflammatory biomarkers may be more important, requiring further research. Similarly, the kinetics of inflammatory biomarkers may provide insights into who will develop postoperative complications. Finally, the practical application of the findings is still unclear. Findings may support targeted management of patients with elevated inflammatory biomarkers before or after surgery, whether through informing heart team approaches (eg, reevaluating procedural choice or timing) or altering postoperative management (eg, closer monitoring or longer hospital length of stay for observation). Cardiac surgery guidelines (eg, coronary, aortic), however, do not describe the role of inflammatory biomarkers apart from specific contexts (eg, inflammatory aortitis).

Future research may explore optimal biomarkers for risk stratification. The authors note that the effect size for CRP may be overestimated, whereas a vascular surgery meta-analysis found no association, suggesting that CRP may not be the best biomarker. Other biomarkers, such as IL-6, show promising preliminary findings but are understudied and may be explored further. In addition, findings highlight opportunities for anti-inflammatory management of cardiovascular disease or patients undergoing cardiac surgery. Indeed, the LoDoCo2 trial [Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease], investigating the use of colchicine, and the CANTOS [Canakinumab Anti-inflammatory Thrombosis Outcomes], evaluating canakinumab, found reduced risks of adverse events in patients with coronary artery disease treated with anti-inflammatory drugs. Multiple trials have explored the use of tranexamic acid compared to placebo in patients undergoing cardiac surgery with significant reductions in inflammatory biomarker concentrations, albeit with considerable study heterogeneity. The Steroids in Cardiac Surgery (SIRS) study evaluated the use of methylprednisolone in patients undergoing cardiac surgery with the use of cardiopulmonary bypass but did not find significant effects on either mortality or major morbidity.

Ongoing trials may shed further light on the role of inflammatory biomarkers and anti-inflammatory management. In Canada, quercetin, a polyphenol with anti-inflammatory activity in vitro, is being studied as part of the Quercetin in Coronary Artery By-pass Surgery (Q-CABG) trial wherein 100 patients are randomised to either quercetin or placebo from 2 days before to 7 days after CABG. Outside cardiac surgery, the Perioperative Inflammatory Response Assessment in 204 High-Risk Patients Undergoing Non-Cardiac Surgery (INSIGHT) study will evaluate the association between postoperative inflammatory biomarkers (CRP, IL-6, procalcitonin) and 30-day and 1-year cardiovascular events in patients at high risk for cardiovascular complications when undergoing noncardiac surgery. Although it is in a distinct patient population, the findings may generate hypotheses for future study in the field of cardiac surgery.

Conclusion

Inflammatory biomarkers may be associated with poor outcomes after cardiac surgery. Though physiologically plausible, further research is needed to better elucidate associations and identify specific biomarkers with highest risks for improved risk stratification. Understanding which patients are at highest risk may inform heart team approaches to and closer monitoring of patients at risk of poorer outcomes.

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