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Renal Implications Following Cardiac Surgery: A Comprehensive Review

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Abstract

Background: Renal complications following cardiac surgery are fairly common and may require renal replacement therapy. Most of such cases recover with either conservative management or temporary, short period requirements for renal replacement therapy. Several studies highlight compelling evidence for such complications to be recognised and managed promptly. Aim: In this review, we aim to address the identified risk factors and pathophysiology of cardiac surgery associated renal injury. Furthermore, data regarding acute kidney injury and the long-term renal complications post-cardiac surgery will also be analysed. Methods: A comprehensive review of literature was conducted using appropriate keywords on search engines of SCOPUS, Wiley, PubMed, and SAGE Journals. Conclusion: Various risk factors during the periods of surgery have been identified to be linked to the occurrence of these adverse outcomes. Many of these factors have been identified through extensive research and are modifiable while several others are still unclear or needs deeper understanding and studies.

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Aim: In this review, we aim to address the identified risk factors and pathophysiology of cardiac surgery associated renal injury. Furthermore, data regarding acute kidney injury and the long-term renal complications post-cardiac surgery will also be analysed.

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Conclusion: Various risk factors during the periods of surgery have been identified to be linked to the occurrence of these adverse outcomes. Many of these factors have been identified through extensive research and are modifiable while several others are still unclear or needs deeper understanding and studies.

Introduction

Renal complications following cardiac surgery are well recognized, with acute kidney injury (AKI) being the most prevalent. Cardiac surgery-associated acute kidney injury (CSA-AKI) has an incidence varying from 7-28% in adult patients.[1] The incidence of AKI in paediatric patients following congenital heart surgery is even higher; with an incidence of 40% in this age group. AKI is also linked to the rapid progression of chronic kidney failure, which poses as long-term renal complications post-cardiac surgery.[2]These adverse outcomes are associated with increased morbidity, premature mortality, longer hospital stays, and incur higher hospital

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fees. Multiple studies conducted, confirm the connection between the severity of AKI post cardiovascular surgery and the probability of death.[3]

Acute kidney injury is generally defined as a rapid deterioration in kidney function resulting in structural and functional damage. AKI normally creates an upsurge in serum creatinine value as well as in blood urea nitrogen concentration. However, due to the delay in the rise of these values, AKI is more commonly manifested clinically by a deterioration in the value of the urine output.[4]

Multiple classification systems are designed to stage AKI. Few common classifications used are the RIFLE or AKIN criteria. RIFLE is the acronym for Risk, Injury, Failure, Loss, and End-stage kidney disease. Patients are classified either by their glomerular filtration rate or urine output. The AKIN classification is essentially a revised edition of the RIFLE with a few important changes; a) elimination of GFR criteria, b) lower serum creatinine threshold for the diagnosis of AKI, and c) reduced duration for diagnosing AKI (changed from 7 days to 48 hours).[3] These criteria rely heavily on serum creatinine which may prove inaccurate as the value has a gap in the rise and involves the reduction of 50% of kidney function in order for it to be elevated in the serum. Hence, several biomarkers are coming to light, such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1, which indicate kidney damage or inflammation. A study by Jayaraman et al. showed that NGAL has a higher sensitivity of detecting intrinsic AKI at 24 hours based on the RIFLE criteria than compared to creatinine.[1]

In our review, we have summarized AKI in further depth relating to its incidence, aetiologies as well as management. Although AKI has been extensively researched, the research on CKD remains fairly minimal. This review also aims to shed light on CKD, its associated risk factors, and methods of reducing the chances of complications.

Pathophysiology

The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI) is not fully understood. However, it is reasonable to accept that several factors contribute to postoperative renal damage. Adverse renal outcomes can be the consequence of several assaults that happened before, during, and after the surgery.[5] A few important mechanisms of CSA-AKI include peri-operative renal ischaemia, reperfusion injury, cardiopulmonary bypass (CPB)-induced haemolysis, pigment nephropathy, oxidative stress, and inflammation.[6] A figure adapted from Yuan et al. has been included in this review to further understand the mechanism of acute kidney injury (Figure 1).[10]

The highly regulated renal perfusion system consists of a shunt that helps maintain electrolyte and water concentration gradients in the renal medulla for tubule and collecting system reabsorption but renders the renal medulla and corticomedullary junction hypoxic relative other tissues. This may act as a protective mechanism for oxidative injury but increases susceptibility to ischemia. Surgery may alter renal perfusion hence damaging tubules at the corticomedullary junction and medulla. Furthermore, aorta cannulation and cross-clamping increase atheroemboli to the kidneys, further exacerbating ischemia, and inducing inflammation. Renal oxygenation may also be impaired due to sympathetic nervous system activation, the endogenous release of circulating catecholamines, and the induction of the renin-angiotensin-aldosterone cascade.[10]

Intraoperatively, many factors may alter renal perfusion, such as the vasodilatory effects of anaesthesia, the usage of diuretics, and blood loss which overall accentuates the effect of hypoperfusion on the kidneys. Following a prolonged period of ischaemia, restoration of blood flow may also cause reperfusion injury in which renal tissues are further damaged due to the induction of oxidative stress. Oxidative stress increases the generation of proinflammatory mediators hence inflicting renal damage.[6] Another cause of renal injury is by nephrotoxins, such as the usage of iodine contrast dye during coronary angiography.[7]

Elevated postoperative plasma concentrations of inflammatory cytokines are significantly associated with a higher risk of developing AKI. Evidence suggests that plasma IL-6 and IL-10 may serve as biomarkers for perioperative outcomes. Although the mechanism behind the inflammation is not completely understood, it may be caused due to a combination of factors including contact activation from the exposure of blood to

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the CBP circuit, ischemia-reperfusion injury, and oxidative damage.[10]

Furthermore, the usage of cardiopulmonary bypass (CPB) itself may evoke renal damage due to the trigger of systemic inflammatory response syndrome (SIRS), the consequences of changes in blood flow and renal vasomotor tone as well as the formation of microemboli. SIRS during CPB is elicited by the contact of blood with the foreign material of the bypass circuit and prompts widespread inflammation and renal damage. CPB also alters the pressure for effective renal blood flow by altering renal vasomotor tone, hence further risking the kidneys to ischemia and reperfusion damages. Haemolysis induced by CPB also worsens SIRS and induces the generation of microemboli, which directly destruct capillaries in the kidneys.[10]

Additionally, both hemoglobinemia and myoglobinemia are independent predictors of postoperative AKI. Billings et al., in their study, demonstrated that postoperative AKI is associated with both enhanced intraoperative hemeprotein release and enhanced lipid peroxidation. The study found that patients who had developed AKI had twice the plasma-free hemoglobin at the end of CPB than those who did not, despite having similar AKI risk profiles and identical CPB durations in each group. Hence, data suggests that hemolysis and high concentrations of plasma-free hemoglobin, through induction of subsequent injurious mechanisms or from direct effects, may contribute to the development of AKI post-cardiac surgery.[12]

Risk Factors

A variety of risk factors have been identified in the past through multiple studies. The occurrence of renal complications after cardiac surgery is a result of multifactorial risk factors that eventually can lead to reduced renal function. For this review, risk factors leading to acute kidney injury have been classified as preoperative, intraoperative, and postoperative as summarized in Table 1.

Preoperative:

Anaemia is recognised as a critical risk factor as it further increases the vulnerability of the kidneys to ischaemia and injury during cardiac surgery.[5] Another predictor for cardiac surgery-associated renal complications is the presence of comorbidities such as insulin-requiring diabetes mellitus, pre-existing chronic kidney disease, and chronic obstructive pulmonary disease (COPD).[1] Pre-existing heart conditions such as congestive cardiac failure and left ventricular heart impairment also predispose to renal complications post-heart surgery.[1, 7] A study by Ortega-Loubon et al. showed that an extremely reduced left ventricular ejection fraction of $<40\%$ is a remarkable risk factor associated with the postoperative renal complication. Moreover, the study also identified other risk factors as being old age and pre-existing kidney disease.[7]

Intraoperatively :

Blood transfusion was discovered to have a harmful effect on kidney function post-surgery. This was hypothesised as the changes in the structure and function of the red blood cells during storage leads to ineffective oxygenation.[8] Another risk factor of CSA-AKI is cardiopulmonary bypass (CPB) itself due to the initiation of systemic inflammation.[5] Prolonged cardiac surgery, aortic cross-clamping, and vasopressors also predispose to renal complications by changing renal perfusion, causing oxidative stress, and inducing inflammation.[3, 5]

Postoperative:

Risk factors are also found tied to the risk of renal complications. The usage of nephrotoxic antibiotics, such as vancomycin and aminoglycosides were found to significantly increase the risk of renal adversity. Hence, the avoidance of using such drugs and administering less nephrotoxic antibiotics post-surgery will reduce the risk of a complication.[8] Hypotension post-surgery, longer mechanical ventilation, and the administration of antihypertensive also amplify the susceptibility of adverse renal outcomes.[7]

Long-term and Short-term Complications of Cardiac Surgery

Aforementioned, acute kidney injury is a long-recognised complication after cardiac surgery resulting in a higher morbid-mortality. The condition is characterized by a sudden deterioration of kidney function indicated by a reduced glomerular filtration rate (GFR). A summary of the studies used for the purpose of

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this review has been provided in Table 2. A retrospective study conducted by Vellinga et al. analysed 565 patients undergoing cardiac surgery for AKI. Results showed that 14.7% of the patients developed AKI with a significant difference in age, preoperative estimated glomerular filtration rate, and chronic kidney disease between the CS-AKI group and the control population[16]

Additionally, perioperative renal dysfunction proves to be a major determinant of both operative and long-term mortality, following cardiac surgery. Postoperative AKI not only extends hospitalization days but also becomes an important independent prognostic risk factor. It is essential to identify high-risk patients for developing AKI in order to provide appropriate support in terms of fluid management, hemodynamic support, adjunctive pharmacologic therapy, or early aggressive use of therapy (RRT).[6]

In patients undergoing cardiac surgery, baseline and pre-existing comorbidities and functional status are important factors that should be taken into consideration as they can determine the likelihood of developing AKI postoperatively. Amini et al., in their study analysed the risk factors of AKI after coronary artery bypass grafting surgery (CABG). Results concluded that patients that developed AKI had longer ventilation times, ICU, and hospitalization days. They also found a strong association between advanced age, diabetes, on-pump surgery, red blood cell transfusion, and prolonged mechanical ventilation and development of AKI.[16] Many of these risk factors such as advanced age, hypertension, hyperlipidaemia, and peripheral vascular disease, and not modifiable.[17]

Mizuguchi et al. demonstrate the occurrence of AKI in patients with no pre-existing kidney disease to be 4.4% and those with pre-existing chronic kidney disease to be 4.8% proving that the degree of AKI can identify patients who will have a higher risk of progression to acute kidney disease.[18] These patients may benefit from a close follow-up of renal function because they are at risk of progressing to chronic kidney disease. Rosner et al. suggest that the usage of preoperative intro-aortic balloon pump in conditions of low cardiac output and insult is associated with the development of postoperative AKI.[19]

A retrospective study conducted by Han et al. concluded that aetiologies responsible for the development of AKI included cardiogenic hypotension (46.3%), multiorgan failure (2.8%), respiratory failure (3.7%), haemolysis (7.4%), drug-induced interstitial pneumonia (0.9%), and other unknown causes (38.9%).[8] Similarly, in 2015, Mao et al. investigated the occurrence, severity, and outcomes of acute kidney injury in octogenarians following heart valve surgery. Nearly half of the cohort studied developed AKI after valve replacement with significant functional impairment and reduced survival.[9] Moreover, aortic cross-clamp, CPB, and blood transfusions and vasopressors are unique to cardiac surgery; however, are associated with an increased risk of developing AKI.

Predominantly, postoperative AKI occurs due to haemodynamic instability, nephrotoxic, inotropic, and vasoconstrictor drugs, and systemic inflammation. Moreover, patients with congestive heart failure or left ventricular dysfunction postoperatively have an impaired ejection fraction, and perfusion pressure to the kidneys and hence are at a higher risk of developing AKI.[19]

Management

Rosner et al. suggest identifying patients who are at high risk for AKI is critical to its prevention and management.[12] This can be carried out by utilizing well-established risk stratification systems for cardiac surgery patients. The best-validated scores predict severe AKI requiring dialysis and include the Cleveland Clinic Score and the Mehta Score.[20,21] Another systematic review reiterated these findings, concluding that the Cleveland Clinic model has been the most widely used and has shown high discrimination in most of the tested populations.[21]

However, a prospective study by Bernie et al. analyzed data from 30,000 subjects undergoing cardiac surgery in the UK to develop a model using KDIGO criteria for predicting all stages of AKI. The model's risk prediction score of any stage of AKI (AUC, 0.74 (95% CI: 0.72-0.76)) exhibited better discrimination compared with the Cleveland Clinic Score and equivalent discrimination to the Mehta Score. This is the first risk score that accurately identified patients at risk of any stage AKI.[23]

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Although preventative strategies are limited, current evidence supports the maintenance of renal perfusion, and intravascular volume while avoiding venous congestion, administration of balanced salt instead of high-chloride intravenous fluids. Additionally, limiting cardiopulmonary bypass exposure.[6] Traditional treatment options mainly focus on attenuating ischemia, reducing intrarenal inflammation, and supportive care. Patients who have developed AKI following cardiac surgery should be enterally or parenterally fed 20-30 kcal/kg/day.[22] In cases where AKI is severe enough to require RRT, higher caloric intake via protein supplementation may be necessary with glycemic control indicated in patients developing AKI.[25, 26]

Cases wherein AKI becomes severe, RRT is required to treat hyperkalemia, remove excess fluid, treat uremia, or reverse acidosis.[27] A meta-analysis conducted by Liu et al. indicated that early initiation of RRT for patients with AKI after cardiac surgery was associated with lower 28-day mortality and shorter ICU length of stay.[27] Likewise, a 2013 study contrasting early versus late RRT initiation in critically ill patients established that early RRT was associated with lower mortality (51.5 vs. 77.9% p=0.001) and reduced time of the ventilator (12.8 vs. 18.9 days, p-0.03).[28]

Of note, failure to respond to RRT may be associated with a combination of risk factors including older age, intraoperative and postoperative blood transfusions, non-emergent surgery, gender, and increased preoperative serum creatinine (s-Cr) and uric acid levels. However, it is widely accepted that the benefits of achieving haemodynamic stability with the use of RRT and potential improvement in renal function outweigh the risks.[20]

Another potential treatment is alkaline phosphatase. Although its exact mechanism of action is unknown, it is likely to be related to dephosphorylation and thereby detoxification of detrimental molecules involved in the pathogenesis of acute kidney injury. Results from a randomized controlled trial conducted in 2012 found that intravenous administration of recombinant alkaline phosphatase increase creatinine clearance from 50 ± 27 ml/minute at baseline to 108 +- 73 ml/minute after treatment in the alkaline phosphatase group versus from 40 +- 37 to 65 +- 30 ml/minute in the placebo group (p=0.01). Despite the promising results, this did not translate into a decreased need for RRT.[30]

Long Term Complications

It is increasingly recognised that AKI after cardiac surgery is associated with long term complications such as CKD and end-stage renal disease (ESRD).[31] The phases of kidney disease progression from normal kidney function through AKI, and CKD have been summarized in Figure 2.[7] Between 0.6% to 5% of cardiac surgery patients will need dialysis postoperatively. This puts them at a higher mortality rate of 25% in contrast to 2% among patients who do not need dialysis.[32] In a study conducted by Lo et al., AKI patients requiring dialysis had a 28-fold increased risk of progressing to stage 4 CKD or ESRD compared to hospitalized patients without AKI.[33] RRT is used for the management of severe AKI or oliguric renal failure. Evidence from trials suggests that RRT lowers the risk of uraemia, hyperkalaemia, and promotes overall haemodynamic stability in cardiac patients.[27] Surgical patients with higher baseline eGFR are more likely to recover with RRT. Despite this, findings from a cohort study examining the likelihood of recovery on RRT revealed that there are fewer benefits available for heart failure patients, regardless of baseline eGFR. This can be due to challenges in fluid management, and potential for haemodialysis induced myocardial injury in heart failure patients. [34]

5.1 Chronic Kidney disease

AKI is recognized to be a strong independent risk factor for CKD progression.[33] Based on the KDIGO guidelines, the diagnosis for CKD is confirmed by at least two eGFR values of [?]60 ml min-1 (1.73m)-2 separated by at least 90 days. According to one study on patients with reversible AKI, the hazard ratio for CKD development was 2.3 in contrast to patients without AKI.[35] This is a serious concern especially after cardiac surgery, due to the poor cardiovascular morbidity and mortality associated with CKD.

The transition from acute kidney disease to CKD is known as “maladaptive repair”. This pathway is characterised by persistent parenchymal inflammation, G2/M arrest in tubular epithelial cells, and epigenetic

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reprogramming of myofibroblasts which predisposes the kidneys to fibrosis and ultimately CKD. [37] Similar to CS-AKI, risk factors for the progression of CKD include having a pre-operative eGFR <80 ml min-1 (1.73m)-2, advancing age (>65yr), type of surgery; aortic surgery or heart transplantation, and an aortic clamping time greater than 50 minutes. Other recurring features they observed among surgical patients with postoperative CKD were that they typically had a higher BMI, were hypertensive, and received more blood transfusion during the intraoperative period.[38]

Moreover, previous studies have highlighted the use of norepinephrine during CPB as another potential risk factor for CKD. Generally, norepinephrine is known to improve renal function in sepsis by promoting creatinine clearance and urine output. However, norepinephrine can also reduce medullary perfusion and oxygen tension, thus causing secondary renal hypoxia injury and diminished renal function.[39]This is of particular concern for patients with congenital heart disease (CHD) undergoing cardiac surgery.[40] It is probable that a combination of any of these risk factors along with the patient's predisposing factors may influence their susceptibility to CKD progression. Table 3 summarises the patient and procedure-related risk factors that result in chronic kidney disease and ESRD.

5.2 End-stage renal failure

It is demonstrated that a dose-dependent relationship exists between increased severity of AKI and increased ESRD incidence among cardiac surgery patients.[31] Of note, small changes in postoperative s-Cr levels resulted in up to a 4-fold increase in long-term ESRD risk. A study by Ryden et al found that patients with reduced preoperative eGFR are associated with a higher absolute risk of ESRD after CABG procedure. Other known factors that predispose ESRD development includes lower left ventricular ejection fraction, previous stroke, myocardial infarction, and heart failure. [32]Not only is diabetes mellitus is one of the principal causes of ESRD, but the trajectory of ESRD is also rapid; within 5 years, among diabetic patients who develop AKI postoperatively [33]

Minimizing complications

Considering the significant renal complications associated with cardiac surgeries, several clinical trials have been conducted in attempts to manage risk factors appropriately and evaluate medical interventions, to improve both short-term and long-term kidney outcomes.[41]

6.1 Pre-operative

Patients may be exposed to contrast agents from clinical procedures prior to having their cardiac surgery. These are known to be nephrotoxic and would, therefore, involve a certain risk of developing contrast-induced AKI (CI-AKI). Newer iso-osmolar contrast agents that are less toxic can be used as an alternative for these procedures. Likewise, factors that alter renal perfusion should be identified and corrected. Nephrotoxic medications should be discontinued. If necessary, perioperative hydration and inotropic agents to improve cardiac output may be used. While intravenous isotonic crystalloid solution could lower CI-AKI risk, excess fluids may potentially cause harm and increase CI-AKI incidence. Whenever possible, renal recovery should be encouraged, and surgery should be delayed to prevent CS-AKI risk.[42] Likewise, pre-operative anaemia is reported to be independently associated with postoperative AKI and should thereby be avoided and managed appropriately before surgery.[27]

6.2 Intra-operative

There is increasing evidence that a low CPB target temperature and a prolonged CPB duration are associated with post-operative KDIGO-3 development, particularly among patients with raised pre-operative serum creatinine levels. Recent studies have suggested that rewarming, rather than cooling, can lead to higher metabolic demand. Longer duration required for the rewarming process further subjects the kidney to ischaemia thereby resulting in renal injury. By raising the target temperature, the risk of KDIGO-3 development can be reduced by 16% per degree Celsius increase.[43]

Furthermore, findings from a prospective randomized controlled trial reported a 22% relative risk reduction

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in the rate of perioperative AKI, after using nitric oxide (NO) instead of nitrogen in patients undergoing multiple valves cardiac surgery. NO is a potent vasodilator and promotes tissue perfusion in the body. Based on this study, prolonged CPB leads to haemolysis, increased plasma Hb concentration, and NO consumption compared to before surgery. By exposing the plasma to 80 parts per million NO gas during and after surgery for an additional 24hrs, plasma NO depletion can be prevented, therefore reducing AKI risk and transition to stage 3 CKD at 1 year and 90 days post-surgery. This occurs due to the oxidization of plasma Oxy-Hb to Met-Hb by NO gas, thus preventing systemic and pulmonary vasoconstriction and kidney injury.[43]

Based on reports from animal and human trials, the accumulation of leukocytes and neutrophils in the kidneys have a protective role in tubular injury in the setting of AKI. Results from a recent meta-analysis of 6 RCTs (n=374) determined that leukocyte filters can reduce the incidence of CS-AKI (OR: 0.18; 95% CI: 0.05-0.64). However, a possible weakness of this study was the small sample size used in the RCTs. Further research is required to validate the efficacy of leukocyte filters in preventing CS-AKI.[45] Similarly, the administration of intraoperative natriuretic peptides to prevent renal ischemia-reperfusion injury, seem to lower the incidence of postoperative AKI in various trials. However, large RCTs are still needed to confirm these findings.[41]

6.3 Post-operative

Due to the complex nature of CS-AKI, it has been suggested that incorporating a combination of interventions would provide greater benefit to cardiac patients postoperatively, rather than a single intervention alone. In 2017, a single-center trial, PrevAKI RCT, was conducted to evaluate the use of KDIGO guidelines in reducing the incidence of postoperative AKI. This study selected high-risk patients with a urinary (TIMP-2)/(IGFBP7) ratio greater than 0.3.[46] Evidence from preliminary data demonstrated that the KDIGO-based bundle of care helped reduce the incidence and severity of postoperative AKI in these patients. Recommendations include avoiding nephrotoxic drugs, preventing hyperglycaemia, and optimizing fluid status and haemodynamic.[46] KDIGO guidelines were also investigated in the ELAIN trial, another single-center RCT, which revealed that early use of RRT led to a decrease in mechanical ventilation time and hospital inpatient duration, as well as an increased rate of recovery by day 90 compared to late RRT use postoperatively.[48]

Future Direction

Managing and minimizing the risk of CS-AKI and long-term renal complications remains a challenging problem. Several clinical trials exploring preventative interventions have been attempted over the years with conflicting results. A potential reason for these inconsistencies could be due to the lack of phenotyping and risk stratification among cardiac surgery patients. Through the use of clinical features (e.g. pre-existing comorbidities, preoperative glomerular filtration rate), genetic, blood and urine biomarkers, patients at higher risk of CS-AKI could benefit from earlier diagnosis and timely management.[41] According to findings from the TRIBE-AKI study, there is a potential use for blood and urine biomarkers to determine the risk of CKD progression among cardiac surgery patients. Elevated levels of these biomarkers in the postoperative setting may improve management and encourage closer outpatient follow-up to those at greater CKD risk.[49, 50]

Conclusion

Renal complications post-cardiac surgery can be detrimental if not recognised promptly. There is a need for extensive trials to validate novel prediction scores and hence minimize the occurrence of the most common complication i.e. acute kidney injury. Similarly, early recognition of AKI can prevent the patient from progressing on to developing long-term complications such as chronic kidney injury.

Human studies: No ethical approval required as no patient information was shared

Data availability statement: The authors confirm that the data supporting this literature are available within the 'reference' section of this paper.

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