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Treatment of acute kidney injury in cancer patients

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ABSTRACT

Acute kidney injury (AKI), either of pre-renal, renal or post-renal origin, is an important complication in cancer patients, resulting in worse prognosis, withdrawal from effective oncological treatments, longer hospitalizations and increased costs. The aim of this article is to provide a literature review of general and cause-specific treatment strategies for AKI, providing a helpful guide for clinical practice. We propose to classify AKI as patient-related, cancer-related and treatment-related in order to optimize therapeutic interventions. In the setting of patient-related causes, proper assessment of hydration status and avoidance of concomitant nephrotoxic medications is key. Cancer-related causes mainly encompass urinary compression/obstruction, direct tumoural kidney involvement and cancer-induced hypercalcaemia. Rapid recognition and specific treatment can potentially restore renal function. Finally, a pre-treatment comprehensive evaluation of risks and benefits of each treatment should always be performed to identify patients at high risk of treatment-related renal damage and allow the implementation of preventive measures without losing the potentialities of the oncological treatment. Considering the complexity of this field, a multidisciplinary approach is necessary with the goal of reducing the incidence of AKI in cancer patients and improving patient outcomes. The overriding research goal in this area is to gather higher quality data from international collaborative studies.

Keywords: acute kidney injury, cancer, CAR T-cells, checkpoint inhibitors, chemotherapy, multiple myeloma, renal replacement therapy

INTRODUCTION

Acute kidney injury (AKI) is the most common renal complication in cancer patients, resulting in a worse prognosis, interruption or cessation of active anti-cancer treatment, longer hospitalizations and increased healthcare costs [1]. AKI alters both the pharmacokinetics and pharmacodynamics of anti-cancer drugs, resulting in suboptimal treatment or increased risk for drug-associated toxicities. It is important to recognize risk factors and causes of AKI in cancer patients in order to initiate specific AKI treatment in a timely manner. The causes of AKI in cancer patients are often multifactorial, including pre-renal, renal and post-renal causes or, alternatively, patient-related causes, cancer-related causes and treatment-related causes [2]. Careful identification of the underlying causes of AKI is important to allow for specific treatment when available. The continuous and rapid introduction of novel oncological therapies is particularly challenging, as novel treatments can be associated with ill-defined renal toxicities. Adequate management of AKI is crucial to improve outcomes in this patient population and

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will allow patients to enjoy the benefits of novel cancer treatments. In this review, a diagnostic approach to patients with AKI and general and cause-specific AKI treatment strategies will be discussed.

THE DEFINITION OF AKI

Kidney Disease: Improving Global Outcomes (KDIGO) defines AKI as any of the following: an increase in serum creatinine to 1.5 times baseline or by ≥0.3 mg/dL (26.5 μmol/L) within 48 h or urine output <0.5 mL/kg/h for ≥6 h [3]. The KDIGO diagnostic criteria for AKI are based on the risk, injury, failure, loss, ESRD (RIFLE) and Acute Kidney Injury Network (AKIN) criteria.

THE EPIDEMIOLOGY OF AKI IN CANCER PATIENTS

The incidence of AKI is significantly increased in cancer patients as a consequence of the cancer itself, its treatment or severe complications [2]. In a Danish population observational study including 1.2 million people followed from 1999 to 2006, the 1- and 5-year risks of AKI (defined by the RIFLE criteria) and AKI failure (tripling of serum creatinine or absolute increase >4 mg/dL) were 17.5% and 27% and 4.5% and 7.6%, respectively [4]. As this is an observational study, no conclusion regarding the causality between cancer (type) and the development of AKI can be made. The risk of developing AKI was highest in the first year after the diagnosis of cancer, especially in elderly patients. Malignancies most commonly associated with AKI were renal cell carcinoma (RCC) (44%), multiple myeloma (MM) (33%), liver cancer (32%) and leukaemia (28%). Also, patients with metastatic disease had an increased risk of developing AKI [4]. AKI requiring dialysis within 1 year of AKI onset occurred in 5.1% of cancer patients with any AKI stage [4]. In 163 071 cancer patients receiving systemic treatment (chemotherapy or targeted agents), the rate of AKI was 27/1000 person-years with an overall cumulative incidence of 9.3% [5]. In this study, malignancies carrying the highest 5-year AKI risk were MM (26.0%), bladder cancer (19.0%) and leukaemia [5]. Additional risk factors for AKI were advanced cancer stage, chronic kidney disease (CKD), diabetes mellitus (DM) and, in patients ≥66 years of age, the use of diuretics and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [5]. In a recent study by Péron *et al.* [6], 2872 patients with metastatic disease receiving systemic treatment from nine European Organization for Research and Treatment of Cancer (EORTC)-sponsored trials were evaluated for the occurrence of AKI. RIFLE events occurred in 40% of patients, and most RIFLE events occurred early during the course of treatment. The occurrence of a first RIFLE event was associated with reduced progression-free survival (PFS), while the impact on overall survival (OS) was heterogeneous [6]. Notably, AKI was not associated with an increased rate of treatment discontinuation but was associated with reduced treatment dose intensity [6]. In a study by Salahudeen *et al.* [1], including 3558 hospitalized cancer patients, 12% developed AKI (using the modified RIFLE criteria) during admission compared with 5–8% in the non-cancer population. In hospitalized patients, the occurrence of AKI was associated with longer hospital stays (2-fold), higher costs (2.1-fold) and a higher risk of death (4.5-fold) [1]. Also, in the intensive care unit, the incidence of AKI is higher in cancer patients and is associated with worse survival rates [7]. The 28-day mortality of cancer patients who require dialysis has been estimated to be 66–88% [1]. Increased mortality has also been observed in cancer patients who developed AKI on top of pre-existing CKD [8]. We can conclude that AKI is a common complication not only in hospitalized cancer patients, but also in outpatient clinics, and is associated with an increased morbidity and mortality.

CAUSES OF AKI IN CANCER PATIENTS

In general, AKI in cancer patients can be patient, tumour or treatment related (Figure 1). Most of the time, AKI in cancer patients is multifactorial.

Patient-related causes

Patient-related causes of AKI in cancer patients include age, sepsis, hypovolaemia (vomiting, diarrhoea), use of nephrotoxic medications and comorbid conditions such as pre-existing CKD, DM, heart failure and cirrhosis [9].

Cancer-related causes

Cancer-related causes include urinary compression/obstruction, direct tumour kidney involvement, multiple myeloma–associated nephropathies, cancer-induced hypercalcaemia, cancer-related thrombotic microangiopathy (TMA) and paraneoplastic glomerulopathies. Glomerular diseases associated with malignancies are rare, heterogeneous (including, among others, membranous nephropathy, minimal change disease, anti-neutrophil cytoplasmic antibody-associated vasculitis and Henoch–Schönlein purpura) and beyond the scope of the current review [10].

Compression and obstruction of the urinary tract can be caused by the primary tumour or by metastases. In most instances, the course of renal function decline in these patients is gradual [11]. Direct tumoural infiltration of the kidney is frequent in lymphoma and leukaemia patients and is more commonly encountered in patients with aggressive and disseminated disease [12]. Up to 90% of patients with lymphoma show evidence of renal involvement in autopsy studies, resulting in increased renal size on radiographic imaging and bilateral interstitial infiltration by lymphoma cells [13]. In leukaemia patients, 60–90% have renal involvement in autopsy studies [14–16]. AKI in the setting of tumour infiltration is the result of tubular compression and disruption of the renal microcirculation [14–16].

Cast nephropathy is an important manifestation of MM and the most common cause of AKI in these patients. In MM patients, free light chains (FLCs) are filtered in the glomerulus and enter the urine at high concentrations, overwhelming the resorptive capacity of the proximal tubules. As a consequence, FLCs arrive in the distal tubules and interact with Tamm–Horsfall protein to form myeloma casts. Both the physical blockage of the distal tubules and the FLC-mediated injury to the proximal tubules contribute to the occurrence of AKI [17, 18].

Cancer-induced hypercalcaemia occurs in 10–30% of all patients with malignancies (most common in MM and squamous cell carcinoma of the lung) [9]. The signs and symptoms of hypercalcaemia are non-specific and therefore its diagnosis is often delayed. Symptoms can include nausea, vomiting, constipation, abdominal pain, anorexia, bone pain, polyuria, fatigue, weakness and, in severe cases, neurologic symptoms such as confusion and coma [19]. Different mechanisms of malignancy-associated hypercalcaemia have been described: secretion of humoral factors (such as parathyroid-related hormone), local osteolysis due to tumour bone invasion and absorptive hypercalcaemia due to excess vitamin D production by malignant cells.

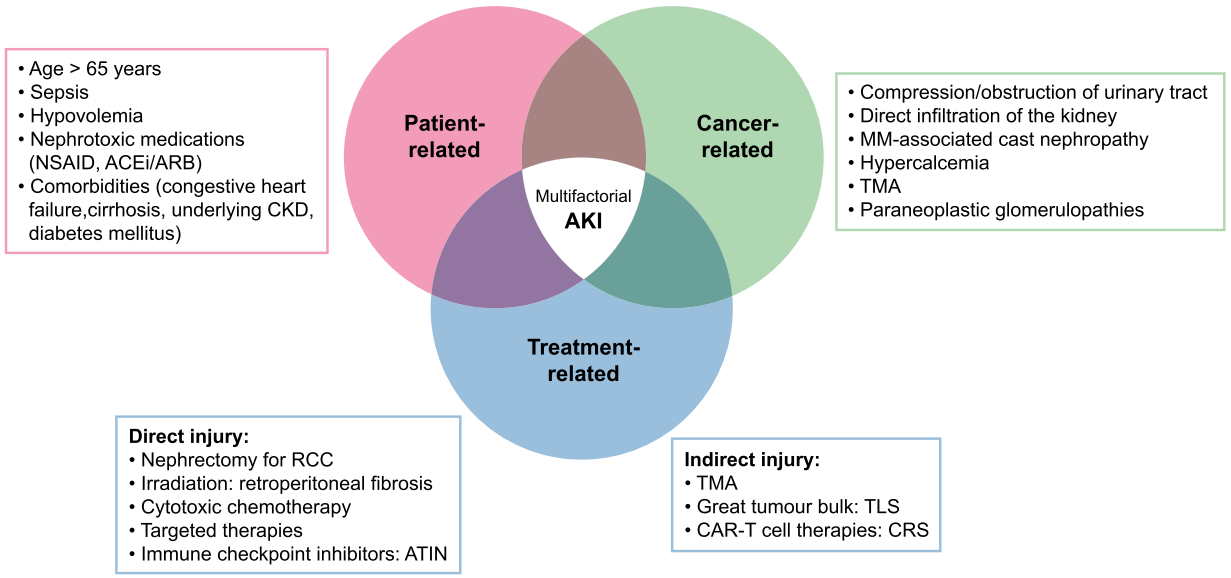

FIGURE 1: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATIN, acute tubulointerstitial nephritis.

The differential diagnosis of TMA in cancer patients is broad. Cancer-induced TMA and drug-induced TMA are the two main aetiologies, but it is important to not rule out the possibility of a separate incidental diagnosis of thrombocytopenic purpura (TTP) or complement-mediated haemolytic uraemic syndrome [or atypical haemolytic uraemic syndrome (aHUS)]. Coombs negative microangiopathic haemolytic anaemia and thrombocytopenia are the typical biochemical features of TMA, characterized by endothelial cell activation. Cancer-induced TMA could be due to systemic microvascular metastases or widespread bone infiltration [20]. Back or bone pain is common [21]. Most cases are secondary to solid organ tumours. Patients with cancer-induced TMA have a poor prognosis. There is no beneficial role for plasmapheresis or immunosuppressive agents [20].

Treatment-related causes

A number of oncologic treatments may induce AKI, either through direct injury to the kidney (as in the case of surgical therapy or post-renal AKI due to fibrosis secondary to radiotherapy or chemotherapy-induced AKI) or through indirect effects, as in the cytokine release syndrome (CRS), tumour lysis syndrome (TLS) and drug-induced TMA [22] (Tables 1 and 2).

Mechanical injury due to surgical interventions is especially seen in the treatment of RCC. In a study of 253 046 RCC patients, 5.5% (14 303 in radical and 3505 in partial nephrectomy) experienced AKI [23].

Among classical cytotoxic chemotherapeutic agents, the ones most commonly related to the development of AKI are cisplatin, mitomycin-C, gemcitabine, methotrexate (MTX), ifosfamide and pemetrexed (Table 1). In an Indonesian retrospective study, Prasaja *et al.* [24] reported the occurrence of cisplatin-associated nephrotoxicity in 88 patients treated with cisplatin ≥60 mg/m^2. Kidney injury was observed after the first cycle and the degree of renal impairment worsened with the increasing number of chemotherapy cycles. In a recent study by Motwani *et al.* [25], the incidence of cisplatin-associated AKI was 12%.

High-dose intravenous MTX, defined as a dose of ≥500 mg/m^2, is a standard treatment for cancers such as acute lymphoblastic leukaemia. MTX and its metabolites precipitate in acid urine (pH < 5.5) within the renal tubules, causing crystal nephropathy, resulting in significant nephrotoxicity in 2–12% of patients [26].

Immune checkpoint inhibitors (ICIs) induce potent anti-cancer effects by unleashing anti-cancer T-cell immunity and have revolutionized cancer treatment in recent years. ICI-associated immune-related adverse events most commonly involve the skin, endocrine organs or gastrointestinal system, while kidneys are rarely affected. In the biggest case–control study to date, Cortazar *et al.* [27] identified lower baseline estimated glomerular filtration rate (eGFR), use of proton pump inhibitors and combination ICI therapy as risk factors for ICI-associated AKI. In this study, ICI-associated AKI occurred at a median of 14 weeks (interquartile range 6–37) after ICI initiation, and most patients had subnephrotic proteinuria and pyuria [27]. Acute tubulointerstitial nephritis is most often seen in biopsies. In a recent large Spanish cohort of cancer patients receiving ICI, Garcia-Carro *et al.* [28] reported an AKI incidence of 15.5% (at an average time of 3.5 months after treatment initiation). In that study, the occurrence of a single episode of AKI was associated with an increased risk of mortality [28].

Chimeric antigen receptor (CAR) T-cell therapies use genetically engineered T cells specifically targeting tumour antigens and are mainly used in the treatment of haematologic malignancies [29]. After recognition of their cognate antigen, CAR T-cells rapidly proliferate, producing large amounts of inflammatory cytokines, possibly resulting in CRS. Severe CRS can result in capillary leak syndrome, multi-organ system dysfunction and pre-renal AKI. Three case series have recently been reported on the characteristics of AKI during CAR T-cell treatment [30–32]. Axicabtagene ciloleucel (Yescarta) is more often associated with the development of AKI as compared with tisagenlecleucel (Kymriah) (19–30% versus 5%, respectively). The different rate and severity of AKI in patients receiving different CAR T-cell products are explained by differences in the induction of CRS. The magnitude of cell proliferation and inflammatory cytokine secretion are dependent on the distinct co-stimulatory

Table 1. Anti-cancer agents associated with AKI

Medication	Main mechanism of action
Classic chemotherapeutics	
High incidence of AKI	
Cisplatin	Inhibition of DNA replication
Ifosfamide	Induction of DNA strand-breaks
Pemetrexed	Inhibition of dihydrofolate reductase
MTX	Inhibition of dihydrofolate reductase
Moderate/low incidence of AKI	
Carboplatin/oxaliplatin	Inhibition of DNA replication
Diaziquone/melphalan/procarbazine/ temozolomide/trabectedin	Inhibition of RNA production
Azacitidine, cladarabine, clofarabine, cytarabine, deoxycofymycin, fludarabine, 5-fluorouracil, gemcitabine, mercaptopurine, thioguanine	Inhibition of DNA production by incorporation of chemically altered nucleotides or by depletion of nucleotides
Chloroethylnitrosourea	Interstrand cross-linking of DNA
Irinotecan	Single-strand DNA breaks
Targeted agents	
Anti-VEGF treatment	Antibody to VEGF or VEGF-R, inhibition of VEGF signalling
Tyrosine kinase or multikinase inhibitors	Inhibition of tyrosine kinase or multikinase signalling
BRAF inhibitors	Inhibition of mutated *BRAF* V600E kinase
ALK inhibitors	Inhibition of mutated ALK
Immunotherapeutic agents	
Immune checkpoint inhibitors	T-cell activation by inhibition of negative co-stimulatory signals
CAR T-cells	T-cell targeting of specific tumour cell antigens

VEGF, vascular endothelial growth factor; VEGF-R, vascular endothelial growth factor receptor; ALK, anaplastic lymphoma kinase.

Table 2. Cancer treatments and TMA causes

Cancer treatment	Potential cause of TMA and solution
Checkpoint inhibitors (e.g. ipilimumab)	ADAMTS13 deficiency; responds to plasmapheresis
Lenalidomide	ADAMTS13 deficiency; responds to plasmapheresis
Gemcitabine	Dose-dependent toxicity; may respond to complement inhibition
Mitomycin-C	Dose-dependent toxicity; may respond to complement inhibition
VEGF inhibitors (e.g. bevacizumab, aflibercept) and tyrosine-kinase inhibitors (dasatinib, sunitinib, ponatinib, etc.)	Dose-dependent toxicity
Proteasome inhibitors (e.g. bortezomib, carfilzomib)	Underlying cause is not known; may respond to complement inhibition or plasmapheresis
Pentostatine	Dose-dependent toxicity
EGFR inhibitor (e.g. cetuximab, gefitinib, erlotinib)	Renal TMA
Calcineurin inhibitor (e.g. ciclosporin, tacrolimus)	Renal TMA
mTOR inibitors (e.g. sirolimus, everolimus, temsirolimus)	Renal TMA
Platinum-based agents (e.g. oxaliplatin)	Drug-induced antibodies
Hormone therapies (e.g. tamoxifen, aromatase inhibitors)	Precipitation of TTP
Allogenic haematopoietic stem cell transplantation-associated TMA	Multifactorial endothelial cell injury + complement activation; Eculizumab? Narsoplimab?

Based on Thomas and Scully [20]. VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin.

domains of the CAR T-cell products [30–32]. Besides AKI, electrolyte disturbances are frequently observed in patients receiving CAR T-cell therapy and most notably hypophosphataemia, hypokalaemia and hyponatraemia. The underlying mechanisms include cortisol release, volume depletion and an interleukin-6 (IL-6)-mediated increase in vasopressin secretion [24].

The risk of TLS is higher in patients with aggressive cancers with a great tumour bulk treated with highly effective treatments such as targeted treatment, monoclonal antibodies, ICI and CAR T-cells.

Drug-induced TMA is rare, but is increasingly recognized as a complication of cancer treatment. If there is slow progressive renal failure, TMA is caused by cumulative dose-dependent toxicity, but if symptoms appear acute with the initiation of the drug, TMA is caused by drug-induced antibodies [21]. Rare cases have shown anti-ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs) antibody-mediated TTP. Finally, transplant-associated TMA is a well-known complication of allogenic haematopoietic cell transplantation (HSCT), with high morbidity and mortality. Various factors in the

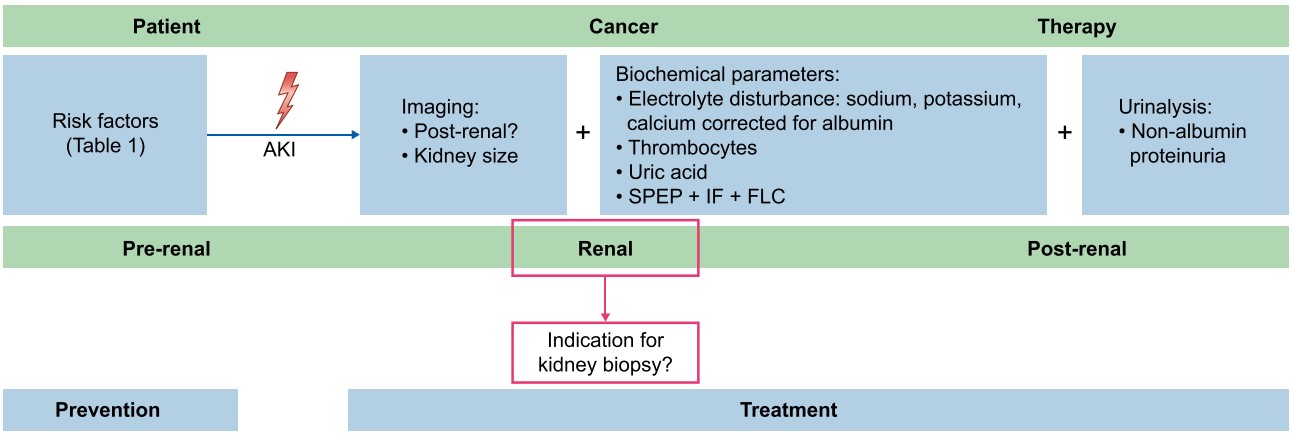

FIGURE 2: IF, immunofixation; SPEP, serum protein electrophoresis.

transplant process can lead to endothelial injury and complement activation [20, 33], including a number of anti-cancer agents (Table 2).

DIAGNOSIS OF AKI IN CANCER PATIENTS

In our opinion, it is important to identify risk factors of AKI, and to make a distinction between patient-related, cancer-related and treatment-related risk factors (Figure 1). This approach will increase the awareness of AKI, possibly resulting in an earlier diagnosis. When a significant decrease in kidney function occurs, renal imaging and urinalysis should be performed. Renal ultrasound (or computed tomography) allows for the identification of post-renal causes of AKI as well as the evaluation of kidney size and vascular structures. Urinalysis should include both analysis of the urine sediment and quantification of urinary protein content. Urinary proteinuria with a negative dipstick analysis is seen in the context of monoclonal gammopathy–associated kidney diseases with urinary loss of FLCs [34]. In 2012, the Kidney and Monoclonal Gammopathy Research Group introduced the term monoclonal gammopathy of renal significance (MGRS) to describe disorders characterized by direct or indirect kidney injury caused by a monoclonal immunoglobulin produced by a B cell or plasma cell clone that does not meet current haematologic criteria for therapy [35]. When an MGRS-associated kidney disease is suspected, identification and quantification of paraprotein should be performed by using serum protein electrophoresis, serum and urine immunofixation and serum FLC measurement. It has been suggested that the diagnosis of cast nephropathy can be made in a patient with AKI and serum FLC levels >50 mg/dL [36]. In a recent study by the Mayo Clinic, the likelihood of diagnosing an MGRS-associated kidney disease in patients with a monoclonal gammopathy increased in patients with proteinuria ≥1.5 g/day, haematuria and an elevated FLC ratio [37]. Besides urinalysis, biochemical tests should be performed, including tests evaluating the presence of TMA and TLS. TTP has to be ruled out (measurement of ADAMTS13 activity), as it has a different treatment. It can be difficult to differentiate between cancer-induced TMA, drug-induced TMA and aHUS, as all are diagnoses of exclusion. Finally, we would suggest considering a kidney biopsy whenever the cause of AKI remains unclear or when a cancer-associated glomerular disease is suspected. Kidney biopsy is a safe procedure (also in cancer patients) and allows for the diagnosis of various renal causes of AKI due to cancer itself or its treatment. Moreover, it may help to know the rate of irreversible loss of kidney function. Currently there are no guidelines for performing a biopsy in cancer patients. We propose a simple flowchart for the diagnosis of AKI in cancer patients (Figure 2).

TREATMENT OF AKI IN CANCER PATIENTS

To improve the prognosis of cancer patients, AKI should be treated without delay and specific treatment should be initiated when available [11].

Patient-related AKI

The treatment of patient-related AKI is beyond the scope of this review, but generally consists of adequate hydration, and therefore weight, blood pressure and urine output should be monitored regularly in cancer patients. Nephrotoxic medications and radiocontrast agents should be used cautiously (Figure 3). The risk of AKI as a consequence of radiocontrast is often overestimated, but not non-existent. In a study by Wilhelm-Leen *et al.* [38], the incidence of AKI in patients to whom radiocontrast was and was not administered was 5.5% and 5.6%, respectively. Therefore, the risk of contrast-induced AKI should be weighed against the consequences of an incomplete diagnostic work-up by avoiding contrast administration. In concordance with the flowchart of Vanmassenhove *et al.* [39], we recommend preventive measures, including intravenous volume expansion with isotonic saline in patients with an eGFR <30 mL/min, in patients with DM or heart failure and an eGFR <45 mL/min or in patients with monoclonal gammopathy. In our practice, we use a regimen of isotonic saline at a rate of 200 mL/h 2 h before and 3 h after the procedure (for a patient of 75–100 kg). Weisbord *et al.* [40] showed no superiority of intravenous isotonic sodium bicarbonate over intravenous isotonic sodium chloride.

Cancer-related AKI

Treatment of post-renal nephropathy. The treatment of ureteral compression/obstruction consists of the placement of a nephrostomy tube or a ureteric stent or an open surgical procedure. Nephrostomy tubes are placed percutaneously under local anaesthesia. Tubes are an efficacious treatment options but require an external collection bag. Double J stents are placed

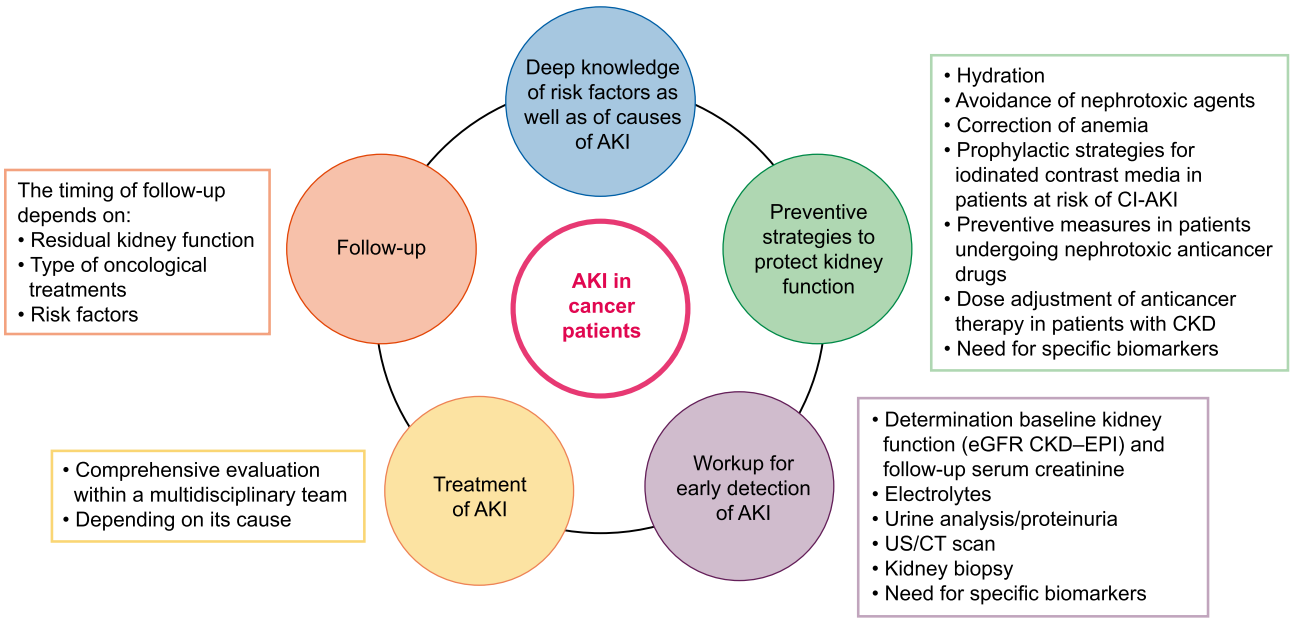

FIGURE 3: CI-AKI, contrast-induced acute kidney injury; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

under general anaesthesia and are associated with a higher failure rate [41]. In one study, the use of ureteral stents in cancer patients was effective to maintain renal function but not to restore it [11]. Treatment of AKI due to direct tumour renal involvement consists of the initiation of appropriate and effective chemotherapy. As renal involvement occurs more commonly in patients with aggressive and disseminated disease, these patients are also at risk for the development of TLS and this should be managed simultaneously (see below).

Treatment of cast nephropathy. Treatment of cast nephropathy in patients with MM consists of adequate hydration in combination with early initiation of cytotoxic chemotherapy to rapidly reduce serum FLC levels. Nowadays, chemotherapy regimens used in this setting include proteasome inhibitors such as bortezomib in combination with thalidomide, corticosteroids, vincristine and adriamycin [42–45]. These regimens have been associated with high rates of improvement in renal function as well as significantly improved survival. Bortezomib is the cornerstone in the treatment of cast nephropathy, as it has been demonstrated to be associated with a rapid improvement in the GFR [46]. The addition of bendamustine to prednisone and bortezomib has also increased renal response rates to >80%, with the majority of responses occurring within 6 weeks [47].

Attempts have been made to improve the outcome of cast nephropathy by using extracorporeal therapies to rapidly reduce the serum FLC concentration, but the results are controversial at best [48]. As far as plasmapheresis is concerned, randomized controlled trials (involving only a limited number of patients) have been performed and generated conflicting results [49]. Case reports and case series generated interest in the use of highly permeable dialysis membranes in patients with cast nephropathy [high cut-off haemodialysis (HCO-HD)]. Recently the results of two phase 2 randomized trials have been reported (MYRE and EuLITE) (Table 3). In the EuLITE trial, there was no benefit noted with HCO-HD over conventional therapy with high-flux HD (HF-HD) in patients who also received a bortezomib-based chemotherapy regimen [50]. In the MYRE trial, some benefit was assigned to the HCO-HD group as dialysis independence at 6 months increased to 56.5% in the HCO-HD arm, compared with 35.4% in the conventional arm ($P = 0.04$) [51]. However, this was a secondary outcome and there was no significant difference in the primary outcome (discontinuation of dialysis at 3 months) in both studies [52, 53]. To date, the benefit of HCO-HD remains unproven and, in our opinion, this treatment approach should only be used in the context of clinical trials and should not delay the initiation of effective cytotoxic chemotherapy [52, 53].

Treatment of hypercalcaemia-induced AKI. An essential step in the initial treatment of hypercalcaemia-induced AKI is intravenous hydration with isotonic saline to improve renal perfusion and allow for increased urinary calcium excretion. Loop diuretics should be avoided unless hypervolaemia is present [19]. Electrolytes need to be monitored because of the possibility of hypernatraemia due to nephrogenic diabetes insipidus [19, 54]. Furthermore, it is important to discontinue any medication that can lead to hypercalcaemia, including a.o. calcium-containing medication, vitamin D, vitamin A, thiazide diuretics, lithium and teriparatide.

Bisphosphonates lower the serum calcium concentration over a period of 2–4 days and prevent recurrent hypercalcaemia. In clinical practice, pamidronate up to 60 mg is infused over 4 h [19, 54]. Pamidronate is more effective in patients with hypercalcaemia due to bone metastasis and less effective in those with humoral hypercalcaemia [19, 54]. However, bisphosphonates can result in nephrotoxicity, and zolendronate should be avoided in patients with a creatinine clearance <30 mL/min. Ibandronate has minimal nephrotoxicity but has not yet been approved for the treatment of hypercalcaemia in cancer patients [19, 54]. Denosumab is also effective and can be safely used in patients with reduced kidney function. The main side effect is hypocalcaemia. Cinacalcet has not been extensively used in the treatment of malignancy-associated hypercalcaemia other than parathyroid carcinoma [55]. Calcitonin is useful in the acute

Table 3. Phase 2 randomized trials with HCO-HD in cast nephropathy

Characteristics	EuLITE	MYRE
Demographics		
Number of patients	43 in the HCO group, 47 in the HF-HD group	46 in the HCO group, 48 in the HF-HD group
Female	40% in the HCO group, 47% in the HF-HD group	50% in the HCO group, 40% in the HF-HD group
Multiple myeloma		
LC only MM	53% in the HCO group, 51% in the HF-HD group	50% in the HCO group; 46% in the HF-HD group
Cast nephropathy	Biopsy-proven	Biopsy-proven
chemotherapy	Bortezomib (1 mg/m^2 on days 1, 4, 8, 11 and 21), doxorubicin and dexamethasone	Bortezomib (1 × 3 mg/m^2 on days 1, 4, 8 and 11) and dexamethasone
Intervention: comparison with conventional therapy with HF-HD	Two 1 × 1 m^2 filter in series (HCO1100; Gambro); 6-h session at baseline, then 8-h sessions on days 2, 3, 5, 6, 7, 9 and 10; from day 12, 8 h sessions on alternate days, reducing to 6-h sessions on alternate days from day 21; 60 g albumin was perfused at each session	Single membrane 2 × 1 m^2 dialyser (Theralite; Gambro); 5 h per session; eight sessions for 10 days, and thereafter three sessions per week if needed, until completion of three cycles of chemotherapy 5 h/session; if serum albumin is <25 g/L before HD, 20 g albumin was perfused after dialysis
Primary outcome:		
Discontinuation of dialysis at 3 months	56% in the HCO group; 51% in the HF-HD group; P = 0.81	41.3% in the HCO group; 33.3% in the HF-HD group; P = 0.42
Secondary outcomes:		
Discontinuation of dialysis at 6 months	58% in the HCO group; 66% in the HF-HD group; P = 0.76	56.5% in the HCO group; 35.4% in the HF-HD; P = 0.04
Discontinuation of dialysis at 12 months	58% in the HCO group; 66% in the HF-HD group; P = 0.76	60.9% in the HCO group; 37.5% in the HF-HD group; P = 0.02
Haematologic response at 6 months	67% in the HCO group; 73% in the HF-HD group; P = 0.46	78.3% in the HCO group; 60.4% in the HF-HD group; P = 0.06
Haematologic response at 12 months	42% in the HCO group; 68% in the HF-HD group; P = 0.02	Not reported
Mortality	At 24 months: 37% in the HCO group; 19% in the HF-HD group; P = 0.03	At 12 months: 20% in the HCO group; 21% in the HF-HD group; P = 0.46

setting, but the calcium-lowering effect is transient due to tachyphylaxis [55]. Calcitonin is given at a dose of 4–8 IU/kg subcutaneously every 6–12 h. Glucocorticoids (hydrocortisone 300–400 mg/day for 3–5 days) are an effective treatment of hypercalcaemia due to the overproduction of calcitriol. Finally, renal replacement therapy (RRT) may be required in the setting of severe hypercalcaemia and AKI with oliguria.

Treatment-related AKI

The decision to temporarily or permanently discontinue oncological treatment depends on several nephrological and oncological factors. The severity of AKI and the extent of renal function recovery, the treatment setting (adjuvant, i.e. curative versus palliative), the possible availability of alternative active treatment options and patients' expected outcome should be taken into account. This further underpins the need for frequent and thorough interactions between nephrologists and oncologists, i.e. the rational basis of the subspecialty of onco-nephrology.

Mechanical injury. Mechanical injury due to surgical intervention is a common complication during radical and partial nephrectomy for RCC. Preoperative assessment of renal function with the identification of risk factors for CKD is important. Furthermore, perioperative awareness about the volume status of the patient and avoidance of nephrotoxic medication are necessary.

The surgical procedure itself is beyond the scope of this article, but the collaboration before surgery and post-operatively between surgeon and nephrologist is essential in preventing kidney injury, and recommendations for pre-surgery evaluation to prevent post-operative AKI and CKD have been recently published [56].

Cisplatin. There is no specific treatment for cisplatin-induced nephropathy at this moment and therefore the prevention of cisplatin-induced nephropathy is key (but beyond the scope of the current review). Amifostine is the only US Food and Drug Administration (FDA)-approved treatment for the prevention of cumulative cisplatin-induced nephrotoxicity [57]. To the best of our knowledge, it is not authorized in Europe. Amifostine is a prodrug of free thiol that interacts with metabolites of cisplatin. Because of important side effects, cost and concerns that it also diminishes the anti-tumour effect, amifostine is rarely used in clinical practice.

MTX. High-dose MTX causes nephrotoxicity, and AKI impairs the renal clearance of MTX, resulting in prolonged exposure to toxic serum levels. Vigorous hydration and urine alkalinization (pH > 7) are mandatory before starting treatment. Furthermore, folinic acid is used to prevent the extrarenal consequences of MTX accumulation. Leucovorin should be started 24 h after completion of each high-dose MTX infusion, and initiation should not be delayed beyond 42–48 h [26]. At the same time, medications that inhibit the folate metabolism (e.g. trimethoprim/sulfamethoxazole), exhibit intrinsic renal toxicity [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), contrast

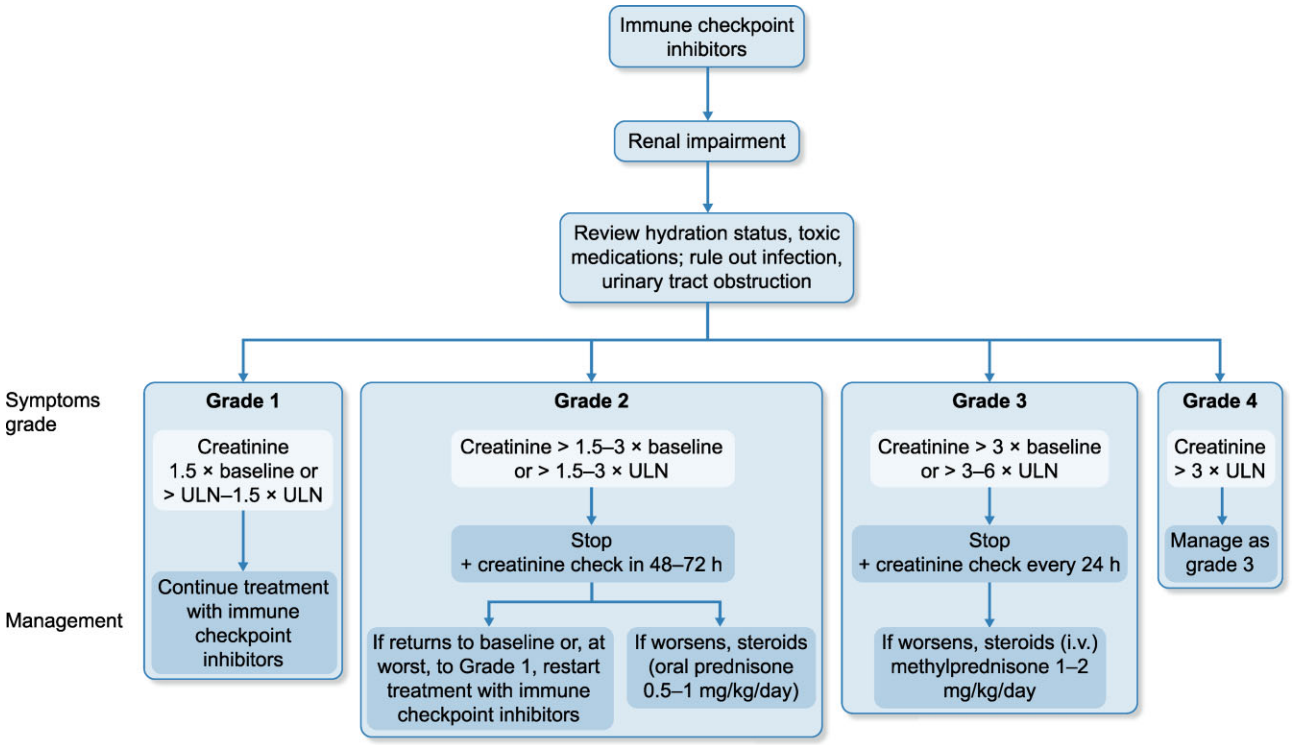

FIGURE 4: ULN, upper limit of normal.

agents] or decrease the fraction of MTX bound to albumin (e.g. aspirin) should be avoided [26].

After infusion of high-dose MTX, therapeutic drug monitoring and serial measurements of serum creatinine, urine output and urine pH are essential to monitor nephrotoxicity. A decline in kidney function is a medical emergency and requires hyperhydration, high-dose leucovorin and, finally, co-administration of glucarpidase when available [26]. Glucarpidase, a recombinant bacterial enzyme that rapidly metabolizes and inactivates MTX, has been demonstrated to reduce MTX plasma levels >98% within 15 min after administration [58]. If the 36-h MTX concentration is >30 μM, the 42-h MTX concentration is >10 μM or the 48-h MTX concentration is >5 μM, and the serum creatinine is significantly elevated relative to the baseline, glucarpidase must be considered. Glucarpidase administration should optimally occur within 48–60 h after the start of high-dose MTX, as glucarpidase is only efficacious intravascularly and life-threatening toxicities may not be preventable beyond this time point [59]. Recently, Truong *et al.* [60] reported five adult lymphoma patients with toxic MTX levels and AKI successfully treated with a single dose of glucarpidase of 1000 U. As far as dialysis is concerned, multiple daily and long dialysis sessions (daily, 4–6 h sessions using HF-HD membranes) are necessary to remove MTX effectively, as MTX is highly protein bound [60]. As MTX has a high intracellular distribution, an important rebound of MTX levels after the cessation of HD is expected.

ICIs. There are currently no evidence-based recommendations regarding the treatment of ICI-associated AKI. Currently available recommendations/guidelines recommend discontinuation of the ICI in cases of significant renal impairment and consideration of systemic corticosteroid therapy (e.g. methylprednisolone 1–2 mg/kg/day). Specific recommendations regarding the dose and duration of corticosteroid treatment cannot be provided at this moment (Figure 4) [27, 61]. A recent meta-analysis suggested that corticosteroid use might hinder the efficacy of ICIs in non-small cell lung cancer patients [62]. Furthermore, the cessation of proton pump inhibitors, NSAIDs and antimicrobials is an integral part of the treatment of ICI-induced AKI [63–65]. The pathophysiology of the toxicity of proton pump inhibitors to renal cells is unknown. It may be due to the oxidative stress caused by necrotic tubular cells [66].

In a multicentre study of 138 patients by Cortazar *et al.* [27], most patients (86%) were treated with steroids and complete, partial or no kidney recovery occurred in 40%, 45% and 15% of patients, respectively. Concomitant tubulointerstitial nephritis–causing medications and treatment with steroids were each associated with improved renal prognosis. Finally, the absence of kidney recovery after ICI-associated AKI was independently associated with higher mortality. ICI was restarted in 22% of patients, and recurrence of ICI-associated AKI only occurred in 23% of rechallenged patients [27].

According to the guidelines, the need and timing of kidney biopsy should be discussed with the nephrologist in difficult cases [63–65]. In our opinion, kidney biopsy is of utmost importance in order to make the correct diagnosis and to guide therapy, because clinical findings and biochemical tests are suboptimal in predicting the underlying kidney lesion [61, 67]. A kidney biopsy should be performed on every patient treated with ICI experiencing AKI when no alternative cause of AKI can be readily identified. Furthermore, proteinuria >3 g/day also warrants a kidney biopsy, as this suggests the presence of an ICI-induced glomerular disorder. Acute tubular interstitial nephropathy is most commonly described on biopsy, but there are multiple causes of kidney injury in cancer patients. If there are no signs

Table 4. TLS risk and management

Cancer type	Low risk (<1%)	Intermediate risk (1–5%)	High risk (>5%)
Lymphoma	Cutaneous TCL, follicular, HL, MALT lymphoma, MCL, MZL	Burkit or lymphoblastic lymphoma: early stage	Burkit or lymphoblastic lymphoma: advanced stage
Acute leukaemia	ALL: low WBCs and LDH	ALL: intermediate WBCs and low LDH	ALL: high WBCs and high LDH
Chronic leukaemia, MM and solid tumours	CML/CLL: chronic phase	CML/CLL: treated with targeted/biologic therapies	
	MM and solid tumours	Chemosensitive, bulky solid tumours	
Prevention/treatment			
Diagnostic measures	No specific measures	Daily labs before and 7 days during therapy	Twice daily labs before and 7 days during therapy
Preventive measures	Moderate hydration	Vigorous hydration Allopurinol/febuxostat to be started >24 h before initiation of therapy and continued until normalization of UA levels and absence of large tumour mass	Vigorous hydration Single 6 mg dose of rasburicase (repeated if needed)
Treatment of established TLS	Admission to ICU for cardiac and biochemical monitoring RRT if necessary (early initiation) Correction of electrolyte abnormalities Vigorous hydration Single 6 mg dose of rasburicase		

TCL, T-cell lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; ALL, acute lymphocytic lymphoma; WBC, white blood cell; LDH, lactate dehydrogenase; CML, chronic myeloid leukaemia; CLL, chronic lymphocytic leukaemia; ICU, intensive care unit.

of immune-mediated lesions, ICI could be continued and administration of steroids could be avoided. Re-exposure to ICI in patients with proven immune-mediated nephritis is an unresolved issue. The approach will depend on the recuperation of the kidney function and the treatment options for the patient.

CAR T-cells. CAR T-cell therapy can cause CRS, but it is also associated with TLS [68]. General treatment strategies are preventing measures and supportive care. Patient selection is important, and in the presence of significant disease burden, TLS prophylaxis is warranted. In the setting of severe CRS, an IL-6 receptor blocker and/or steroids may reduce adverse effects. It is still unclear if immunosuppressive treatment might impair the anticancer treatment.

TLS. The prevention and treatment of TLS is important, especially in patients with aggressive cancers and great tumour bulk treated with highly effective treatments such as targeted treatment, monoclonal antibodies, ICI and CAR T-cells [69]. Identifying patients at high risk of developing TLS on the basis of the presence or absence of cancer- or patient-specific risk factors is important (Table 4) [69, 70]. Rasburicase is approved by both the FDA and the European Medicines Agency (EMA) for the treatment of TLS. It metabolizes uric acid to soluble allantoin, which is rapidly excreted by the kidney, resulting in a rapid and dramatic decrease in serum uric acid levels [71]. A single course of rasburicase is indicated in paediatric and adult patients with leukaemia, lymphoma and solid tumour malignancies who are receiving anti-cancer therapy expected to result in TLS. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, as its use in these patients will result in the development of haemolytic anaemia [72].

HD is an effective therapy for TLS and is also able to correct electrolyte and acid–base disturbances, especially in the presence of oliguric AKI. The need for HD to treat TLS has declined since the introduction of rasburicase.

Drug-induced TMA. If TMA is diagnosed in cancer patients, the cancer treatment must be considered as a potential cause and the culprit agent must be stopped. Plasma exchange therapy has no benefit in drug-induced TMA, except in cases with antibodies against ADAMTS13 [20]. There is limited evidence for the use of complement therapy in the management of drug-induced TMA. There are only case reports available describing the use of eculizumab in drug-induced TMA, suggesting that complement dysregulation has a role in the underlying pathophysiology [73]. For HSCT-associated TMA, recent studies have confirmed the role of complement activation and treatment is shifting towards complement inhibition with eculizumab and mannan-binding lectin serine protease 2 inhibition with narsoplimab [74].

RESEARCH NEEDS

In general, good evidence is lacking in the field of onconephrology, as no or few randomized controlled trials have been performed to date in this research area. For this reason, a lot of the recommendations/suggestions provided in this review are based on evidence from case reports and case series. Specialists in this field should organize in order to perform analyses on larger groups of patients from centres around the world. A good example is the recent international effort to gather data on ICI-induced AKI from Gupta *et al.* [75]. As cisplatin is a widely used chemotherapeutic with an increased risk of AKI, we would urge for additional studies to identify effective approaches to prevent and treat cisplatin-induced AKI. Also, the effective management of cancer treatment-related TMA is a matter of debate, and additional studies are needed in this area. In general, there is an important need to develop onconephrology as a subspeciality in nephrology in order to assemble international collaborative

networks interested in moving this field forward and improving patient outcomes.

CONCLUSIONS

AKI is a common complication in patients with cancer, and its incidence is highest within the first year after cancer diagnosis. Causes include patient-, cancer- and treatment-related factors, and AKI in cancer patients is most often multifactorial. In cancer patients, AKI is associated with a worse prognosis, interruption and/or dose reduction of potentially active treatments, longer hospitalizations and increased costs. Knowledge of the causes and risk factors of AKI is essential for its prevention, prompt identification and adequate treatment (Figure 3). The continuous introduction of novel anti-cancer treatments is particularly challenging, as novel therapies are expected to further improve cancer patients' outcomes but are also frequently associated with novel, and often ill-defined, (renal) toxicities [76]. In our opinion, a multidisciplinary approach is essential to reduce the incidence of AKI and to enhance assessment, prevention, early treatment and monitoring of complications, thus improving outcomes of patients with cancer. A close collaboration between oncologists and organ specialists is also important to enrich the knowledge about oncological therapies and the management of specific toxicities.

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AUTHORS' CONTRIBUTIONS

P.B., G.V.R.S., B.S. and L.C. contributed to the conception and design of the study and to the literature review. P.B. and B.S. performed the literature search and construction of the tables and figures. All authors contributed to data interpretation and writing of the manuscript and all authors reviewed and approved the final version.

CONFLICT OF INTEREST STATEMENT

B.S. is member of the CKJ editorial board.

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