Point-by-Point Response to the Reviewers Comments on Manuscript NO.: 80194, Review Article

Firstly, we would like to thank the Editors and Reviewers for their great efforts and time spent in reviewing this work to improve its quality.

Secondly, the responses to the instructions from the Editors are considered during preparation and submission of the revision files as per recommendations outlined in the first decision letter.

Thirdly, the responses to the reviewers' comments are presented as point-by-point report as following (Changes or corrections are performed in the text and they are highlighted in grey in the copied text after the responses below).

Fourthly, we would like to ask to put the tables at the end of the text to preserve the current sequence of cited references in the text and tables.

Responses to Reviewers Comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: The narrative review proposed by Gadelkareem et al is potentially interesting, focusing on a relevant topic. However, it lacks of supporting data and gives the feeling of a text book chapter for medical students.

I would strongly suggest to include proper citations with larger amount of data and some comparative tables summarizing pros and cons of PCN vs JJ stenting. Also, I find some lexical choices rather questionable for a scientific journal.

Responses:

1) The manuscript has been revised for grammar and writing by the authors and by check using an online program (Grammarly). Specifically, the text has been reviewed for lexical choices that may be unsuitable for scientific publications and suspicious terms have been replaced with scientific ones. Changes are now highlighted in grey within the text.

2) A separate paragraph at the end of Introduction section has been added to mention the scope and brief methods of this narrative literature review.

3) Data withdrawn from the targeted literature have been added in a tabulated form to summarize the pros and cons of PCN vs JJ stenting for malignant ureteral obstruction, either in the research during the last 2 decades (Table 1) or in the procedural work and outcomes (Table 2).

4) Proper references have been cited for the added data and to the previous text to strengthen the values reported from the literature.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this review article, the authors discuss treatment options for obstructive uropathy related to malignancy which is an important topic. Over all article is written well. I would recommend abbreviating and streamlining the manuscript with more focus on available treatment modalities. It will be good to provide a table comparing the pros and cons of nephrostomy vs ureteral stent.

Responses:

1) Many paragraphs have been removed from the sections of pathophysiology and Clinical presentation to abbreviate and streamline the manuscript, focusing on the management and approaches of intervention described in the literature. The removed paragraphs were in Page 5; first paragraph in etiological classification of AKI, Page 6; first paragraph of pathophysiological mechanisms of Po-AKI, Page 7; third paragraph (about CKD with malignancy); Page 9; third paragraph (about the clinical presentation of other types of AKI)

2) Pros and cons of PCN and ureteral stenting have been provided in tables with data summarize the relevant studies published in the last 2 decades (Table 1) and comparison with each other (Table 2).

Highlighted text for changes made for revision

Abstract

There is a well-known relationship between malignancy and impairment of kidney functions, either in the form of acute kidney injury or chronic kidney disease. In the former, however, bilateral malignant ureteral obstruction is a surgically correctable factor of this complex pathology. It warrants urgent drainage of the kidneys in those patients presented in the emergency settings. However, there are multiple controversies and debates about the optimal mode of drainage of the bilaterally obstructed kidneys in these patients. This review addressed most of the concerns and provided a comprehensive presentation of this topic from the recent literature. Also, we provided different perspectives on the management of this viable subject to facilitate the difficult practical situations of clinical practice under the guidance of solid scientific basis. Despite the frequent trials of improving the success rates and functions of ureteral stents, placement of a percutaneous nephrostomy tube remains the most recommended tool of drainage due to bilateral ureteral obstruction, especially in patients with advanced malignancy. However, the disturbance of the quality of life of those patients remains a major unresolved concern. Beside the unfavorable prognostic potentials of the underlying malignancy and the various risk stratification models that have been proposed eventually, the response of the kidney to initial drainage can be anticipated and evaluated by multiple renal prognostic factors, including the increased urine output, serum creatinine trajectory, and time-to-nadir serum creatinine after drainage.

Key words: Acute kidney injury; Kidney; Malignancy; Percutaneous nephrostomy; Ureteral obstruction; Ureter

Core tip:

Acute kidney injury due to malignant ureteral obstruction is a complex nephrological and urological emergency. Its management includes an initial resuscitation of the metabolic abnormalities, minimally invasive drainage of the obstructed kidneys, and lastly correction of the underlying etiology. Several

prognostic models have been proposed to clarify the best approach. However, there are controversies about the optimal mode of drainage of the kidneys, regarding the tool and laterality of drainage. Despite the practical preference of using the percutaneous nephrostomy rather than the Double-J stent, the optimal mode of drainage has not been defined yet. The parameters of kidney response to drainage and the status of the underlying malignancy are important prognostic factors.

INTRODUCTION

The acute kidney injury (AKI) is defined as an increase in serum creatinine (SCr) of ≥0.3 mg/dl or >50% from the baseline[1,2]. Classically, this biochemical definition is practically translated into a rapid deterioration of the kidney functions within hours or days. It is a reversible pathology when properly and timely managed. According to the positional relationship between the original pathology and the kidney of the affected patient, AKI has classically been classified into prerenal (hypovolemic), renal (intrinsic), and postrenal (obstructive) AKI (Po-AKI)[2-4]. The latter class represents a urological emergency, when the patient presents with disturbed kidney functions, such as an elevated SCr level. The underlying pathology of the Po-AKI is the obstruction of both kidneys or one kidney in patients with a solitary functioning kidney. The obstruction can occur at any point along the course of the ureters. This obstruction can be caused by either benign causes such as urolithiasis or malignant causes such as bladder cancer. Kidney obstruction with elevated functions warrant drainage of the kidneys as fast as possible. Methods of drainage include placement of ureteral stents or percutaneous nephrostomy (PCN) tubes. Considering these variables, there has been no consensus on the optimal mode (method and laterality) of drainage in these cases[5,6]. The malignant ureteral obstruction (MUO) represents a more complex entity than the benign obstruction in the field of AKI, because the former has a mechanical factor which is the obstruction and a metabolic factor which is a mere component of malignancy. These variables have generated a lot of controversies in the different aspects of the management of patients with AKI due to malignant bilaterally obstructed kidneys (BOKs). They may affect the decision-making for the mode of drainage, uncertainty of renal responses after drainage, benefits in the management of the underlying disease, and effects on patient quality of life with the different methods of drainage[6-8]. In this commentary review, we will address these different aspects in patients with Po-AKI due to MUO.

The relevant recent literature in the last two decades was reviewed for the available approaches of drainage of BOKs in patients with MUO. The scope of the review was the clarification of the efficiency of these approaches and the differences and

similarities between them. The relevant findings from the literature are summarized as relevant findings per study (Table 1) and as a comparison of the technical and practical characteristics (Table 2). Many prognostic and risk stratification models have been proposed so far. They are based on variables from the patient and underlying pathology. However, the sharp stratification of these patients and solid guidelines has not been settled yet. These reviewed findings will be addressed and discussed in the different sections of this review.

INCIDENCE

The incidence of AKI has approximately been estimated by The National Institute for Health and Care Excellence as 13–18% of people admitted to hospital[45]. It mainly involves the elderly and has a mortality rate of 10–80%[45,46]. Globally, AKI affects over 13 million people per year and results in 1.7 million deaths. Four in five cases of AKI occur in the developing world[47,48]. Po-AKI (Po-AKI) represents 5-10% of all AKI cases[49]. However, it can represent up to 22% of AKI cases among the elderly[50], and 7.6% of the intensive care patients. Po-AKI due to MUO may represent up to 10% of cases with AKI and 18% of patients with malignancy diagnosed within 1 year[51].

PATHOPHYSIOLOGY

Etiological classification of Po-AKI

The Po-AKI is caused by urinary tract obstruction, when this obstruction affects both functioning kidneys, a solitary kidney, or an only-functioning kidney. Relative to the origin of the obstructing pathology, the mechanism and causes of ureteral obstruction are classified into extraluminal compression, stenosis due to a mural pathology, and intraluminal lodgments. The three most common causes of renal obstruction in adults are urinary stones, malignancy, and iatrogenic benign strictures[6,7]. Hence, these causes are either malignant or benign pathologies. The benign causes include urinary tract stones, ureteral strictures, and retroperitoneal fibrosis[7]. However, the malignant causes include both urological and extraurological malignancies [5,6]. The urological carcinomas of the urinary bladder[10,52] and prostate cancer[18] are the most common causes of MUO. The

extraurological malignancies include colorectal cancer[5], cervical and uterine cancers[27], adnexal cancers, and systemic malignancy such as lymphoma and metastases[5,51].

Pathophysiological mechanisms of Po-AKI with MUO

Obstruction-based mechanisms: There are multiple intrinsic pathophysiological mechanisms of AKI with BOKs, including hemodynamic instability, microcirculatory disorders (such as endothelial dysfunction and microvascular thrombosis), inflammation, tubular cell injury, renal venous congestion, tubular obstruction, and auto-immune processes[53]. Reductions in renal blood flow represent a common pathologic pathway for decreasing glomerular filtration rate in all these mechanisms[54]. However, the most likely explanation is that one adopting an occurrence of alterations in the glomeruol-tubular dysfunctions due to urine flow obstruction[55].

At the few early hours of obstruction of the kidney, the intraluminal pressure is transferred to the renal tubules and to Bowman's space[55]. The transferred pressure results in a decreased filtration pressure in the glomerular capillary walls. After 2-3 hours of obstruction, a prostaglandins-mediated myogenic change in the afferent arterioles increases the renal blood flow, which normalizes within 5 hours. After one day, the renal and intraglomerular blood flow decrease as a result of the intrarenal production of thromboxane A2 and angiotensin II. These products are strong vasoconstrictors of the afferent and efferent arterioles and contribute to the reduction of the glomerular filtration rate[55]. Thromboxane A2 and angiotensin II cause contraction of the mesangial cells, decreasing the glomerular surface area that is used for filtration. After two days, increased thromboxane A2 reduces kidney plasma by 60%. With persistence of obstruction, more losses occur in the tubular brush epithelia and renal blood flow[56].

Alterations in physiological sodium and water reabsorption are noted also. Sodium absorption increases in the proximal tubules, but this increase is associated with a more significant decrease in sodium absorption in the juxtaglomerular nephrons. Also, there is a reduction in the medullary ability to concentrate urine to only 350–

400 mOsm[51,55,57]. This decrease in tonicity results in a drop in water absorption in the descending part of the loop of Henle. Metabolic acidosis and hyperkalemia are common in Po-AKI due to many factors, representing a failure of renal acidification. This occurs with the inability to excrete potassium and hydrogen, which is explained by distal renal tubular acidosis and Na-K-atpase failure, resulting in hyperkalemia[51].

Malignancy-based pathophysiological mechanisms: There is a well-established relationship between malignancy and impairment of renal functions. These intimate relationships have led to the evolution of a new branch of nephrology that concerns associations of cancer with renal disease. It is not only malignancy affects the kidney function by ureteral obstruction, but also various nephropathies are associated with its hematopoietic, chemotherapeutic, immunotherapeutic effects of different types of malignancy. These nephropathies manifest clinically as proteinuria, hematuria, hypertension, and cancer related-chronic kidney disease[58-60].

AKI in patients with malignancy is common. According to a study conducted on about 37 thousands of malignancy patients and over a 5-year period, 27% of those patients developed AKI, and 7.6% of them developed severe AKI required dialysis. Also, the risk of AKI within the first year after a cancer diagnosis can be more than 17% in malignancy patients[61]. The non-obstructive causes of AKI in patients with malignancy include sepsis due to low immunity and bad general conditions, direct kidney injury due to the primary malignancy, metabolic disturbances, and nephrotoxic effects of chemotherapies. In turn, AKI increases the risk of toxic effects from systemic chemotherapy, threatening their continuation[62].

The development of ureteral obstruction in the course of any malignancy is considered as a sign of disease progression and reduces the median survival to < 1 year[21,24,34]. MUO is a bad event that is usually associated with advanced, and often, incurable stages of malignancy. Further, it is a definitive cause of urosepsis, acute pain, and uremic syndrome. Unilateral or bilateral MUO is due to extrinsic compression or direct infiltration by a local primary tumor or retroperitoneal lymphadenopathy. It may occur in patients with a previously diagnosed malignancy up to 84%. The median patient age at MUO diagnosis is usually high (Table 1) and

the median time for development of MUO after the diagnosis of primary malignancy is variable[5,23].

In comparison, the obstruction-based mechanisms seem to have a more favorable prognosis than the malignancy-based mechanisms. Its effect is usually uni-factorial and reversible by a prompt drainage of the kidneys. In contrast, the malignancy-based mechanisms is virtually multi-factorial and irreversible in most instances[62]. Hence, MUO is a modifiable risk factor of morbidity and mortality in patients with Po-AKI due to malignancy. Drainage of the obstructed kidneys can prevent the major sequelae of the obstruction-based mechanisms, promptly reversing the acute deteriorations of renal functions within days or weeks[5].

CLINICAL PRESENTATION

In Po-AKI, the clinical presentation includes the general manifestations of uremia and manifestations of urinary tract obstruction. The latter may include loin pain secondary to stretching of the urinary collecting system and hematuria caused by obstructing malignancy[63]. Decrease in urine output is a common presentation, but it is not specific to Po-AKI[41,51]. Patients with Po-AKI may present with loin tenderness and fever, when obstruction is associated with infection[51,57].

DIAGNOSIS

The initial laboratory evaluation should include measurement of blood gases and electrolyte levels, SCr, blood urea nitrogen, and complete blood count. Urinalysis may be requested in cases with a preserved urine output. Then, AKI could be diagnosed and staged according to KDIGO guidelines. In Po-AKI, the hallmark of diagnosis is the presence of hydronephrosis in abdominal ultrasonography (US) or computed tomography[41]. Hydronephrosis can easily be demonstrated by the grey scale US where pelvicalyceal dilatation is recognized with or without disappearance of the renal papillae[51]. After 3 to 4 weeks of obstruction, diffuse thinning of the renal cortex and the medullary tissue is mostly recognizable. Moreover, Doppler US can evaluate the blood perfusion of the kidneys themselves by measuring the resistive index and ureteral obstruction by evaluation of the ureteral jets. The absence or decreased frequency of ureteral jets may indicate urinary obstruction. The

severity of ureteric obstruction can be determined by evaluating all jet dynamics, including velocity, duration and frequency[64]. However, computed tomography is still the most diagnostic tool of Po-AKI due to benign and malignant causes[5].

MANAGEMENT

Initial measures of management

While the management of the prerenal and renal types of AKI is mainly supportive in nature, drainage of BOKs is the cornerstone of management of Po-AKI. However, the initial conservative management of patients with Po-AKI is mostly similar to that of the other types. It consists of resuscitation and correction of the metabolic imbalances[41]. However, temporary drainage of BOKs is a mandatory and principal intervention, keeping the correction of the underlying cause to a time after recovery from the AKI. A urethral catheter placement can be performed in cases of bladder outlet obstruction such as BPH, but PCN or double-J stent (JJ) are the usual methods in the cases of ureteral obstruction[2,4,65]. Then, the broad-line goals of management are to correct the biochemical abnormalities such as severe metabolic acidosis and hyperkalemia, prevent further injury or progression to chronic kidney disease, and treat the underlying pathology[65]. The management of hyperkalemia includes prevention of the life-threatening cardiac arrhythmias by administering calcium-based salts, support of shifting potassium into the cells, and enhancement of elimination of potassium through cation exchange resins[65,66]. Despite their fundamental roles, these pharmacological and conservative interventions may have a lower effect in the management of Po-AKI than in the management of the other types, relative to the role of drainage [51,57].

Renal replacement therapy is considered in specific circumstances, such as the progression of complications in the severe cases with pulmonary edema, persistent hyperkalemia, and disturbed consciousness. This therapy is mostly in the form of intermittent hemodialysis, but peritoneal dialysis may be performed in a few circumstances[41,51,67]. Regarding the practical aspect of prioritizing dialysis over drainage, there is a perspective, whether the degree of elevation of SCr alone is an indicator to resort to dialysis before drainage[41]. It can be preferable to drain one or

both kidneys, whenever the patient can withstand the intervention for placement of a PCN[5]. This might augment the chances of recovery with the conservative management and in those patients who may still warrant temporary dialysis after drainage. Despite the drainage efficacy, dialysis also could play an important role in the management of those patients, especially when drainage is not preferable such as in patients with very poor prognosis[52,68].

Drainage of BOKs

Currently, there are no consensuses or well-established guidelines addressing the proper drainage of MUO, leading to wide variations in the practice patterns and preferences[5,69,70]. However, relieving MUO prevents death from a progressive renal failure and possibly prolongs the patient survival[20,24]. There are two modalities for drainage of the kidneys with MUO; PCN and JJ. Both methods can cause considerable morbidity and reduce patient's health–related quality of life (QoL). There are multiple studies that compared both of them and their impact on QoL in MUO, because those patients are usually in late stages and their QoL is already impaired[9,71].

The use of JJ for drainage of BOKs has many challenges, including the higher invasiveness, need of anesthesia, liability of obstruction, and impossible placement due to complete obliteration of the ureteral lumen. These limitations are potentially present with antegrade and retrograde placement[72,73]. These challenges lead to the development of the JJ characteristics, ranging from the new materials to the pressure-based capabilities. The JJ has different types, ranging from the conventional polymeric stents to the malignancy-specifically designed ones. Among the latter, there are 3 important types that have gained popularity in the last years and being used in MUO, tandem ureteric stent (TUS), metallic stent and metal-mesh ureteral (MMU) stents. Many studies have concluded very high rates of stent failure in MUO because the tumor or lymphadenopathy compresses the ureter against the indwelling stent, persistently obliterating this tube lumen and limiting the extraluminal flow[74,75]. Also, the ureteral stent promotes mucous production from

the urothelium and in addition leads to urothelial sloughing, the lumen of a ureteral stent can become occluded with these debris[76-78].

Metallic ureteral stents gained superiority over the conventional JJ as it has a low occlusion rate, high success rate (60%) at 1 year and low failure rate (15.4%)[79]. Considering that the median survival time with extrinsic MUO is about 1 year[24,34], there is a high possibility that metallic stent replacement is unnecessary during these patients' life. TUS consists of a side-by-side ureteric stents within the ureter, can resist obstruction by providing a space in-between the two stents that is difficult to compress. It has a success rate of approximately 87% at about 2 years[80]. It has a range of exchange from 6 months to 1 year[76,80]. Success rates ranged from 88% for the Allium stent to 65% for Memokath 051. Resonance stent demonstrated the lowest migration rate (1%). Uventa showed the lowest obstruction rate (6%). A comparative study conducted by Chen et al.[81] reported that metallic stents have longer indwelling time and superior to conventional polymeric stents. There is a mean increase in functional duration of 4 months, using the Resonance stent when it is compared to conventional polymeric stent[75].

Although PCN has a high success rate[13] and considered safer than JJ[69], its need to carry an external bag could threaten the patient QoL[69]. PCN seems to be more suitable for patients with advanced malignancy who may do not have the candidacy for anesthesia or the ureteral patency to pass JJ. Also, they may have expected survival rates less than 12 months that could be improved by PCN. However, the disturbance of their QoL is still the main concern, warranting estimation of the balance between the benefits with the risks[6,70].

There are no clear advantages between the two forms of urinary diversion in MUO[6] (Table 1 and 2). However, the type of urinary diversion depends on the experience of the urologist, the existing expertise, the availability of the armamentarium, the stage of malignancy, and the urgency of the diversion[82]. In addition, it is dependent on the potential benefits of diversion at different parameters, including the radiological exposure, decrease in SCr, the overall complication rate, febrile episodes after drainage, tube exchange rate, and overall patient's survival. Both drainage forms

seem to have no advantage over each other in these variables[43]. However, despite the evidence-based recommendation by the recent meta-analyses in favor of the use of JJ rather than PCN in patients with MUO[43], there is an attitude that PCN is more commonly used than JJ for drainage of BOKS with MUO (Table 1). This attitude is noticeable in the single-center studies[5,8,83]. Owing to the potentials of placement of wide-caliber tubes and insertion of antegrade JJ [11,37], PCN may provide the chance of getting high drainage capacities[44]. Also, PCN may become the only suitable methods for drainage, especially in the elderly, patients with advanced stages of malignancy who are not candidates for intervention[34,43], or have non-passable MUO[15,43]. On the other hand, PCN may disturb the QoL more than JJ[6,19]. This may be attributable to many potential unfavorable events with PCN such as the repeated slippage, obstruction, and urinary leakage. Hence, there should be a sufficient rationale to perform urinary diversion by PCN in patients with terminal stages of malignancy[6,57,84]. If the evidence of the effect on QoL is absent, the potential survival benefit remains the individual factor which drives the decision, whether to perform the diversion, which should be PCN in patients with advanced malignancy[43,84]. This may be attributed to that most of those patients may have no further oncological treatment chances following the diversion[39].

Laterality of drainage of BOKs with MUO has been addressed by some authors like Hyppolite et al.[85] who concluded superiority of bilateral over unilateral drainage. However, Nariculam et al.[28] found no difference between unilateral and bilateral drainage. The combination of the tool and side of drainage in cases of BOKs is known as the mode of drainage. Despite the continuous research, the definition of the optimal mode of drainage of BOKs is still controversial, including the cases of MUO[5,43,70]. We may adopt the perspective of performing a unilateral drainage of BOKs, unless there are indications for bilateral drainage such as bilateral infections, pain and non-improvement of SCr after unilateral drainage. In the latter situation, bilateral drainage can be performed consecutively[5]. Similarly, the optimal type of drainage of BOKs due to BUO is still controversial. In a recent survey study to evaluate the preferences of the urologists and radiologists who may have the principal duties of interventions in cases of acute BOKs, the conclusion was to

individualize the decision for each case with emergency indications for upper tract decompression by JJ versus PCN[86].

PROGNOSTIC PARAMETERS AFTER DRAINAGE OF BOKs DUE TO MUO

Urine output

An increase in urine output is an early sign of renal recovery in patients with oliguric AKI. This is accompanied by a reduction in the level of high SCr, followed by a plateau period, and subsequently a fall in SCr[8,54]. Usually, the increase of urine output is usually physiologic and self-limiting within the first 24 h after relief of obstruction. The kidneys try to normalize the internal environment of the body by fluid and electrolyte homeostasis within the early hours, before returning to the normal status of the urine output[57].

The post-obstructive diuresis means increased urine output after relief of status of BOKs. It is defined as increased urine output >200 ml for two consecutive hours or urine output >3000 ml per 24 h after relief of obstruction. When this diuresis becomes excessive or is prolonged, it becomes pathologic. It is attributed to the sudden release of the obstruction which initiate a reflex diuresis by multiple mechanisms, evoking the full capacity of the functioning nephrons[57]. There is a perspective that post-obstructive diuresis may be a sign of the acuteness of the condition and the magnitude of the renal power preserved. Also, it is believed that it is more common after drainage of BOKs due to BUO than those due to MUO[5]. For example, an obstruction by a stone is related to its migratory potentials that can be sudden and complete in comparison with an infiltrating malignancy that causes a gradual obstruction[6,7]. However, this point of difference between BUO and MUO has not been sufficiently addressed in the literature. Despite its favorable prognostic values, the potential pathologic metabolic and circulatory risks of post-obstructive diuresis may threaten the patient's life. Hence, it should be managed properly by oral or intravenous fluid compensation and management of the electrolyte imbalances that could ensue with excessive diuresis[57].

SCr trajectory

The rate of change of SCr over time in AKI is known as creatinine trajectory. It can be applied in both the deterioration and recovery phases[1,5]. Joining the time factor in this topic may reflect its practical importance in catching a cure in patients with MUO. SCr trajectory has attracted the attention in the management of patients with prerenal and renal AKI[87]. However, it is still not recognizable in cases of Po-AKI. Our own work in this point has not been published yet.

The SCr trajectory is a potential parameter to understand AKI during both the renal dysfunction or recovery phases. The deterioration SCr trajectory may facilitate clinical classification and subtyping of AKI, using a different parameter rather than maximal SCr change. However, it mandates knowing a pre-deterioration or baseline SCr level, which is often lacking for most patients admitted to the emergency settings [1,88]. On the other hand, based on SCr trajectory, the post-intervention classification facilitates understanding patient responses to early medical interventions. This could be provided by serial measures of SCr. Hence, the identification of AKI subclasses based on SCr trajectory has been proposed as a tool to improve the precision of risk stratification of patients with AKI [1,87,88].

The time-to-nadir SCr

The time needed to reach a nadir SCr or what is known the time-to-nadir SCr after drainage of BOKs is another parameter of the responses of the kidneys to drainage. To the best of our knowledge, this parameter has not been sufficiently addressed in the literature of Po-AKI due to MUO. However, our work in this issue has revealed that large proportions of those patients may fail to reach a normal nadir SCr due to the burden of malignancy. Also, the time-to-nadir in cases of MUO seems to be longer than that in the cases of BUO[5]. Furthermore, the long time-to-nadir SCr may be associated with a low pre-drainage low urine output and high body mass index. The rationale of measurement of the time-to-nadir SCr in patients with AKI is related to the magnitudes of benefits provided by early recovery, regarding the chance of cure or early management. This issue is till controversial in patients with MUO. The time-to-nadir SCr may be significantly shorter in patients with potentials

to have a normalized SCr than that in patients without normalized SCr levels after drainage[89].

Malignancy-related factors

The literature reports that some malignancies are considered as statistically significant predictors of worse survival (Table 1). They include the unresectable or unsuitable malignancies for chemotherapy[83], gastro-pancreatic[90], and hormonal-resistant prostate cancers, and those requiring hemodialysis before the procedure[16]. Despite the successful drainage of BOKs in cases of MUO, the survival rate is still poor[23]. The 3 significant factors that can predict a short survival time after PCN in patients with advanced stage malignancy are a low serum albumin before placement of PCN (3 gm/dl or less), low grade hydronephrosis (grade 1 or 2), and a large number of events related to malignant dissemination (3 or more). Patients who had only 1 variable had a 69% chance of 6-month survival, those had 2 variables had a 24% survival rate, and those with 3 variables had a 2% survival rate[6,26]. Wong et al.[23] identified other predictors as metastases, prior therapy, and diagnosis of MUO with a previously established malignancy. Despite developing these prognostic models, there should be a shared decision-making approach to perform invasive procedures like PCN and JJ, with a questionable degree of the effect on renal function recovery, while there can be a plenty of complications. There should be a proper explanation of prognosis, subsequent treatment possibilities and expected results before proceeding to these invasive maneuvers[42].

CONCLUSION

AKI due to MUO is a urological emergency, warranting immediate evaluation and management. The principal line of treatment is the drainage of the kidneys via a placement of PCN or JJ. Despite the growing relevant literature, there is no consensus on the optimal approach. Several prognostic models have been attempted to stratify those patients relative to the potential risks and justify the interventions, but the controversies are persistent. Hence, the decision-making should be suitable to the patient stage and status rather than to be strict to certain guidelines that might be controversial. This selective approach may be attributed to the presence of many

prognostic factors that should be considered during management, including the QoL and the anticipated benefit of drainage with a markedly reduced life expectancy of those patients.

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Table 1: Summary of studies of reporting drainage of BOKs due to MUO during the period 2000-2022

Study		Patients			Underlying Pathology		Drainage	Outcomes			
Authors, year	**Type**	**Number**	**Age mean ± SD or median (range) in years**	**Men/ Women No.**	**Nature of obstruction (No.)**	**Primary site (IC & EC); Type of malignancy (No.) F1**	**Tool/Approach**	**Laterality; Unilateral (No.)/ Bilateral (No.)**	**Technical success rate**	**Overall patient survival time and survival rate**	**Preference/ Conclusion/ Recommendation**
Pappas et al., 2000[9]	Retrospective, comparative	159	65.1 (18–94)	102/57	BUO (30), MUO (125) & Unknown (4)	IC; Bladder & prostatic (NA) EC; GIT & Gyn (NA)	PCN vs JJ	149/10	99% for PCN 81% for JJ	227 days	PCN is safe and effective Mean SCr improved from 6.9 to

											2.2 mg/dl
Ekici et al., 2001[10]	Retrospective series	23	55 (25–76)	21/2	MUO	IC; Bladder only (23)	PCN	NA	100%	4.9 months	PCN is safe to avoid uremia
Chitale et al., 2002[11]	Retrospective cohort	65	NA (53–84)	52/13	MUO	IC; Bladder (30) & prostatic (28) EC; Cervical (4) & rectal (3)	Retrograde (24) vs PCN/Antegrade JJ (41)	NA	PCN; 100% JJ; 21%/98.3%	1-year survival rate was 54.8%	Two-stage antrgrade JJ is preferred
Chung et al., 2004[12]	Retrospective cohort	101	61.4 (33–90)	44/57	BUO (11) & MUO (90)	IC; Renal (2), bladder (2) & prostatic (5)	JJ	65/36	95%	NA	40.6% JJ failure at 11 months; in 50% was due to compression

						EC; GIT (35), uterine (8), ovarian (5), pancreatic (2), lymphoma (12), breast (13) & other (6)					
Ku et al., 2004[13]	Retrospective, comparative	148	57.3 (20-84)	68/80	MUO	EC; NA	PCN (80)/ JJ (68)	108/40	98.7/89 %	NA	PCN is superior to achieve decompression
Danilovic et al.,	Retrospec	43	50.8	16/27	MUO	IC (7);	JJ initially;	39/4	9% (for	NA	PCN might

2005[14]	tive cohort	(25–84)		(25) & BUO	Ureteral (1), bladder (1) & prostatic (4) EC (36); Uterine (9), ovarian (2), colorectal (4), & other (3)	if failed, PCN was placed	IC)/ 53% (for EC)		be better for patients with EC
Ganatra et al., 2005[15]	Retrospec tive cohort	157	54.7 (23–83)	NA	MUO	IC; Bladder (2) EC; Ovarian	PCN (24) / JJ (133)	NA	64.3%	11-month survival rate was 75.8%	Bladder invasion predicts failure of JJ placement

					(26), cervical (16), GIT (32), breast (8), testicular (6) &others (68)					
Romero et al., 2005[16]	Retrospective cohort	43	52 (22-88)	14/29	MUO	IC; Bladder (10) & prostate (5) EC; Cervical (23), ovary (7) & vulva	PCN	NA	100%	Mean 12-month survival rate was 24.2%	PCN drainage is better to those with age <52 years

						(2)					
Rosenberg et al., 2005[17]	Retrospective, comparative	28	51 (21–78)	1/27	MUO	IC; None EC; Uterine (14), ovarian (4), GIT (9) & breast (1)	Retrograde JJ; PCN alternative	NA	92%	15.3 months; 14 patients died from malignancy during study	JJ is recommended to avoid dialysis Mean SCr improved from 2.9 to 1.2 mg/dl
Uthappa, Cowan, 2005[18]	Retrospective cohort	30	61.4 (29-90)	19/11	MUO	IC; Renal (2), ureteral (1), bladder (5) & prostatic (5)	Retrograde JJ; Antegrade JJ was alternative	10/20	50%	NA	Retrograde JJ initial method

					EC; Ovarian (4), uterine (5), rectal (3), testicular (1), GIT (2), & breast (2)					
Wilson et al., 2005[19]	Retrospective cohort	32	68.1 (24-84)	16/16	MUO	IC; Bladder (8) & prostatic (9) EC; Gynecological (7), colorectal	PCN; JJ was a second step in 32 patients	12/20	100%	87 days	PCN is best initially and recommended when there is a definitive plan for treatment

						(7) & breast (1)					
Radecka et al., 2006[20]	Retrospective cohort	151	73.1 (51–97)	112/39	MUO	IC; Renal (4), ureteral (7), bladder (43) & prostatic (55) EC; Gyn (11), colorectal (16) & others (15)	PCN	45/106	NA	255 days; 80% died with PCN	PCN for safety and cost
Kanou et al., 2007[21]	Retrospective, comparat	75	62.7 (36-90)	30/45	MUO	IC; Bladder (4) &	PCN (24) / JJ (51)	NA	100/72.5; only 78.4% of	5.9 & 5.6 months for PCN	Initial trial of JJ without side holes,

	ive				prostate (11) EC; Uterine (25), GIT (28), ovarian (4), retroperitoneal (2) & lymphoma (1)			those started with JJ completed	& JJ, respectively	PCN is alternative
Rosevear et al., 2007[22] F1	Retrospective cohort	54	61 (32–82)	27/27	BUO & MUO	IC; Prostatic (5) EC; GIT (18), lymphom	Retrograde JJ	21/33	81	Mean 16 months	Retrograde JJ considered first line for MUO due to EC

						a (15), ovarian (50, uterine (6) & others (4)					
Wong et al., 2007[23]	Retrospective cohort	102	62 (31–86)	45/57	MUO	IC (30); Bladder & prostatic EC; Gyn (32), GIT (21), lymphoma (5) & other (14)	PCN/Retrograde JJ	77/25	94%; 99% & 84% for PCN & JJ, respectively	6.8 months; 12 month rate was 29%	Prognostic factors; PCN, metastases & MUO diagnosis in established malignancy
Ishioka et al., 2008[24]	Retrospective cohort	140	57 (31–85)	60/80	MUO	IC; Urothelial (13) EC;	PCN	138/2	100%	96 days; 12-month rate was	Risk stratification of patients relative to 1-

						Gastric (29), colorectal (34), ovarian (6), cervical (30) & other (23)			12% Mean SCr improved from 4.33 to 1.39 mg/dl	3 risk factors
McCullough et al. 2008[25]	Retrospective comparative	57	69.5 (40–91)	31/26	MUO	IC; Bladder (12) & prostatic (20) EC; Gyn (8), colorectal (7), lymphom	Retrograde JJ; PCN alternative	NA	54%	SCr improved by 50% immediately after drainage	SCr level at presentation can predict success of retrograde JJ

						a (2) & others (8)					
Lienert et al., 2009[26]	Retrospective series	49	71 (36–91)	27/22	MUO	IC; Bladder (18) & prostatic (15) EC; Colorectal (6), Gyn (5), sarcoma (2), pancreatic (2) & breast (1)	PCN	38/11	100%	174 days; 53% (prostatic) and 82% (non-prostatic) patients died during study	Risk stratification of patients; relative risk factors to validate the prognostic model of Ishioka et al.
Mishra et al., 2009[27]	Retrospective, comparat	15	44.5 (30–65)	0/15	MUO	EC; Cervical (15)	PCN; JJ alternative	1/14	100%	NA	Bilateral temporary PCN help

	ive										receive definitive or specific therapy and avoid dialysis Mean SCr improved from 7.5 to 0.9 mg/dl within 1-3 weeks
Naricula m et al., 2009[28]	Retrospec tive, comparat ive	25	71 (51–85)	25/0	MUO	IC; Prostatic only	PCN	7/18	100%	NA	Unilateral and bilateral PCN drainage were similar 7.5-month Mean SCr

											improved from 612 to 187 µmol ml^{-1} within 14 days
Jalbani et al., 2010[29]	Prospective	40	NA (21–70)	20/20	MUO	IC; Bladder (10) & prostatic (5) EC; Cervical (15), ovarian (2), rectal (3), gall bladder (1), breast (1) &	PCN	20/20	100%	350 days for IC and 25 days for EC	PCN excellent initial intervention Mean SCr normalized in 62.5%

						lymphoma (3)					
Kamiyama et al., 2011[30]	Retrospective series	53	61 (32-92)	22/31	MUO	IC; Prostatic (3) EC; GIT (31), Gyn (13), breast (3), lymphoma (3)	JJ as initial tool	20/33	95.3%	Drainage success 66%	Proposed algorithm of drainage based on primary site, performance status and degree of hydronephrosis
Migita et al., 2011[31]	Retrospective series	25	61 (29–76)	13/12	MUO	EC; Gastric (25)	Retrograde JJ (15); PCN alternative (5)	4/21	80%/100%	5.8 months; 1-year survival rate was 32%	Initial trial should be with JJ Prognosis is usually poor;

										urinary diversion should be tailored per patient
Song et al. 2012[32]	Retrospective, comparative	75	57.1 (20–85)	0/75	MUO	EC; Uterine (26), cervical (26), ovarian (20) & other (3)	Retrograde JJ; PCN alternative	66/9	81.3%; for PCN 100%	9.1 months	Retrograde JJ first-line option; with serum cystatin C >2.5 and obstruction length >3cm, PCN is alternative
Misra et al., 2013[33]	Retrospective, case series	22	75.1 (54–87)	20/2	MUO	IC; Bladder (6), prostate	PCN; Antegrade JJ second step in 10	11/11	100%/77%	78 days	PCN is effective, but with significant

						(12), EC; Gyn (2) & rectal (2)	patients				morbidity and not prolonging life; Decision of drainage made after full discussion
Cordeiro et al., 2016[34]	Prospective	208	61 (19 – 89)	101/107	MUO	IC; Bladder (47) & prostatic (25) EC; Cervical/ uterine (51), ovarian	Initial retrograde JJ (58); PCN as alternative (150)	107/101	27.9%/ 100%	144 days; 1-year survival rate was 44.9% and 7.1% for favorable and	Risk stratification model with three groups to determine usefulness of urinary diversion; favorable, intermediate

						(10), colorectal (45) & other (30)				unfavorable groups, respectively	and unfavorable
Efesoy et al., 2018[35]	Retrospective series	362	43.2	203/159	BUO & MUO (151)	IC; Bladder (31) & prostatic (43) EC; Cervical (57), uterine (6), ovarian (5) & rectal (9)	Ultrasound-guided PCN; Seldinger or direct puncture techniques	293/61	96.1%	NA	Ultrasound-guided PCN is recommended procedure
Tan et al. 2019[36]	Retrospec	89	50.3	0/89	MUO	EC;	Retrograde	67/22	77.5%/	100%	No

	tive, comparative	(25–78)	Cervical (89)	JJ; PCN alternative	100%	differences between JJ and PCN outcomes. Drainage using JJ is preferred generally, but PCN is better in patients with severe hydronephrosis and long-segment ureteral obstruction (>3cm)

Tibana et al. 2019[37]	Retrospective, comparative	41	65.6± 9.5	23/18	MUO	IC; Bladder (12) & prostatic (9) EC; Uterine (11), ovarian (1), colorectal (7) & retroperitoneal (1)	PCN; Antegrade JJ	10/16	NA	NA	Antegrade JJ is alternative to PCN and retrograde JJ Clinical improvement in 97.5%
Haas et al., 2020[8] **F**[2]	Retrospective database study	238,528	65.5± 14.6	47.6%/52.4%	MUO	IC; Bladder (9.8%), prostatic (17.9%) &	Retrograde JJ (18%)/ PCN (11.4%)	NA	NA	Death in hospital rate was 7.3%	There was a substantial variation in approaching MUO with

					other (4.2%) EC; GIT (24.3%), Gyn (20.8%), lymphoma (10.3%) & other (15%)					temporal decline in use of JJ, but steady use of PCN with higher use in metastatic cases Patients with urologic malignancies were older
De Lorenzis et al. 2020[38]	Retrospective, comparative	51	70 (58–76)	20/31	MUO	EC only; Colonic (28), rectal (14), gastric (5), pancreatic	Retrograde JJ; PCN	30/21	80.4%/ 100%	10.5 months; survival rate was 15.7%	GIT cancers causing MUO are associated with poor prognosis

						(3) & appendicular (1)					
Folkard et al., 2020[39]	Retrospective multicenter series	105	68.8 (30–93)	55/50	MUO	IC (54); Bladder & prostatic EC (51); Gyn, colorectal & other	PCN; Antegrade JJ second step in 62%	46%/54%	100%	139 days; 4-year survival rate was 24.8%. Only 30.5% underwent further oncological treatment	Mean SCr improved from 348 to 170 µmmol/L
Izumi et al.,	Prospecti	300	68	126/174	MUO	IC;	PCN (44)/	161/13	NA	Median	Risk

2021[40]	ve multicenter comparative	(25–96)	Bladder (19), ureter (13), prostatic (12) & other (6) EC; Gyn (66), GIT (121), lymphoma (26), other (37)	JJ (217)	9	survival times (1-year survival rate) of the good, intermediate and poor risk groups were 406 (54.4%), 221 (32.7%) and 77 (8%) days,	stratification proposed based on primary site of malignancy, laterality of MUO, SCr level & treatment for primary site (PLaCT); Good, intermediate & poor risk groups

									respectively	
Gadelkareem et al., 2022[5]	Prospective, non-randomized	107	56.6	68/39	BUO (53) & MUO (54)	IC; Bladder (30) & prostatic (5) EC; Colorectal (11), cervical (6) & lymphoma (2)	PCN (79) & JJ (28)	57/50	98.3%/96.6%	NA	PCN is more suitable to MUO Mean SCr imrpved from 6.1 to 1.2 mg/dl
Kbirou et al., 2022[41]	Retrospective cohort	102	60 (36–84)	0/102	MUO	EC; Cervical (95), uterine (5) & ovarian	PCN (94) / JJ (8)	NA	100%	NA; 88% of patients had normali	PCN is the main tool of drainage Early diagnosis

					(2)				zed kidney function	may enable prevention of MUO
Pickersgill et al., 2022[42]	Retrospective cohort	78	NA	NA	MUO	EC;	JJ; PCN alternative	NA	Median (range) of JJ exchange was 2 (0–17)	19.9 months	JJ failure was high, warranting early use of PCN in management of MUO

F1 Underlying malignancies were classified according to the primary site or origin as malignancy from the urological system which was named intrinsic cancer and malignancy from other or distant systems or organs which was named extrinsic cancer.

F2 The values of the subtypes of malignancy are provided as percentage due to the large number of cases.

Abbreviations: BUO; Benign ureteral obstruction, EC; Extrinsic cancer, IC; Intrinsic cancer; GIT; Gastrointestinal tract, Gyn; Gynecological, JJ; Double-J stent, MUO; Malignant ureteral obstruction, PCN; Percutaneous nephrostomy, NA; Not available/accessible data, No.; Number of patients, SD; Standard deviation, SCr; Serum creatinine, UTI; urinary tract infection.

Table 2: Comparison between the drainage of kidneys with MUO by PCN versus JJ approach

Variables F[1]	Drainage by PCN	Drainage by JJ
Design of catheter		
Manufacturing characteristics	One-end coil kidney tube, with a need for fixation to the skin or change by a Foley catheter after tract establishment Material: Polymeric materials	Two-coil self-retaining internal ureteral catheter Material: Different, including polymeric and metallic types
Route of drainage	Drain the kidney to outside the body	Drain the kidney to urinary bladder
Length	Suitable to the skin-to-pelvicalyceal distance	Suitable to the ureteral length
Mechanism of drainage	Catheter lumen only	Ureteral lumen plus catheter lumen
Procedure/Technique		
Armamentarium required	Needs radiological or ultrasonographic localization of the target calyx	Needs endoscopic armamentarium; C-arm and cystoscope
Approach	External and artificial	Internal and natural/artificial (antegrade)
Anesthesia	Mostly local	Local, epidural or spinal
Feasibility	Independent on ureteral patency Equally feasible to external internal MUO	Dependent on ureteral patency More feasible to external (compressive) MUO
Procedural time	Longer	Shorter

Preference and indications	The advanced stages	The early stages
Success rate	High; Up to 96–100%	Relatively low, up to 85%
Drainage and complications		
Complications	They are dependent on the non-natural route (more invasive), with a greater incidence of injury of adjacent organs, hemorrhage, discomfort, obstruction and accidental tube displacement	They are dependent on the internal route, with higher possibilities of LUTS, UTI, hematuria, and potential obstruction by underlying malignancy
Mechanism of failure of drainage	Mainly due to lumen obstruction by thick urinary contents and tube slippage	Mainly due to compression of the ureteral and stent lumens by the underlying malignancy
Effects on the outcomes		
Kidney drainage and decompression	No statistical differences, but it is better with PCN, especially with infections	Lower efficacy
Normalization of functions	No difference	
Patient survival	No difference	
Hospital stay	Longer	Shorter
Periodical change of catheter	No difference	
Overall rate of complications	No difference	
Potential effect on quality of life	Higher due to external nature of urine drainage	Lower due to internal nature of drainage

F[1] The variables, classifications and information provided in this table are withdrawn from the current literature, specifically they are framed within the last two decades[9,12–14,17,21,33,43,44]

Abbreviations: MUO; Malignant ureteral obstruction, JJ; Double-J stent, LUTS; Lower urinary tract symptoms, PCN; Percutaneous nephrostomy, UTI; Urinary tract infection.