REVIEW ARTICLE

Effects of Pulmonary Hypertension and Right Ventricular Function in Short and Long-Term Kidney Function

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Abstract: Background: Pulmonary hypertension is not uncommon in patients with renal disease and vice versa; therefore, it influences treatments and outcomes. There is a large body of literature on pulmonary hypertension in patients with kidney disease, its prognostic implications, economic burden, and management strategies. However, the converse, namely the hemodynamic effects of pulmonary hypertension on kidney function (acute and chronic kidney injury) is less studied and described. There is also increasing interest in the effects of pulmonary hypertension on kidney transplant outcomes.

The relationship is a complex phenomenon and multiple body systems and mechanisms are involved in its pathophysiology. Although the definition of pulmonary hypertension has evolved over time with the understanding of multiple interplays between the heart, lungs, kidneys, etc; there is limited evidence to provide a specific treatment strategy when kidneys and lungs are affected at the same time. Nevertheless, available evidence appears to support new therapeutics and highlights the importance of individualized approach.

There is sufficient research showing that the morbidity and mortality from PH are driven by the influence of the pulmonary hemodynamic dysfunction on the kidneys.

Conclusion: This concise review focuses on the effects of pulmonary hypertension on the kidneys, including, the patho-physiological effects of pulmonary hypertension on acute kidney injury, progression of CKD, effects on kidney transplant outcomes, progression of kidney disease in situations such as post LVAD implantation and novel diagnostic indices. We believe a review of this nature will fill in an important gap in understanding the prognostic implication of pulmonary hypertension on renal disease, and help highlight this important component of the cardio-reno-pulmonary axis.

Keywords: Pulmonary hypertension, acute kidney injury, chronic kidney disease, transplantation, pathophysiology, PAH.

1. INTRODUCTION

Pulmonary Hypertension (PH) is clinically defined by a mean Pulmonary Artery (PA) pressure of 25 mm Hg or more at rest, as measured by right heart catheterization [1]. These high pressures in the vasculature of the lungs can be idiopathic or secondary to various clinical conditions. Bearing in mind the diverse processes involved in pathology of the pulmonary vasculature, the 5th World Symposium on PH in Nice, France (2013) recommended classifying PH into five groups: [1] Pulmonary Arterial Hypertension (PAH); [2] PH due to left-sided heart disease; [3] PH due to chronic lung disease and/or chronic hypoxia; [4] Chronic Thromboembolic PH (CTEPH); [5] PH with unclear or multifactorial mechanisms [1, 2] (Table 1).

Group 2 and Group 3 pulmonary hypertension are the most prevalent forms of pulmonary hypertension complicating heart failure and lung disease respectively [3]. For example, PH is a common feature of heart failure, affecting at least 70% of heart failure patients, and it has been shown that the onset of PH in heart failure is associated with a doubled increased risk of mortality from heart failure [4-7]. Similarly, several studies have shown that when Chronic Obstructive Pulmonary Disease (COPD) is associated with PH, the mortality was also twice as high as when COPD occurred with normal pulmonary pressures, even after adjusting for confounders such as lung function variables, blood gasses, and age [8-11]. PH is under-diagnosed and diagnosis is often made late with a median survival of only 2.8 years [12]. A diagnosis of PH also increases the cost of inpatient admissions; a study found that the aggregate cost of hospital visits of a patient in the United States with the principal diagnosis of PH increased 209.5% from $301,324,218 in 2000 to $932,554,725 in 2013 [13].

There is sufficient evidence that morbidity and mortality from PH are driven by the influence of the pulmonary hemodynamic dysfunction on the kidneys. This review aims at examining the patho-physiological effects of pulmonary...
hypertension on Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD), with pointers at possible areas for intervention.

1.1. Effects of PH on AKI

1.1.1. Definition of AKI

The definition for AKI used in clinical and epidemiologic studies is based on specific criteria that have been sequentially developed. The KDIGO definition and staging system are the most recent and preferred definition [14]. Other criteria include the RIFLE criteria [15] and a subsequent modification proposed by the Acute Kidney Injury Network (AKIN) and others [16-18].

The KDIGO guidelines define AKI as follows which is currently the most utilized [14]:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or

- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or

- Urine volume <0.5 mL/kg/hour for six hours.

The KDIGO criteria allow for correction of volume status and obstructive causes of AKI prior to classification. Before diagnosing and classifying AKI, one should assess and optimize volume status and exclude obstruction. The timeframe for an absolute increase in serum creatinine of ≥0.3 mg/dL is retained from the AKIN definition (48 hours), while the timeframe for a ≥50 percent increase in serum creatinine reverted to the seven days originally included in the Acute Dialysis Quality Initiative (ADQI) RIFLE criteria.

1.1.2. Role of PH in AKI

There is some agreement in the literature that the primary mechanism through which PH leads to kidney dysfunction is through an increase in Central Venous Pressure (CVP) or

| Causes | 1 – PAH | 2 – PH Due to Left Heart Disease | 3 – PH Due to Lung Disease and/or Hypoxemia | 4 – Chronic Thromboembolic PH | 5 – PH with Unclear and/or Multifactorial Mechanisms |
|--------|---------|---------------------------------|---------------------------------|-------------------------------|---------------------------------|
| a. Idiopathic: Heritable, BMPR2; Heritable, ALK1, endoglin, SMAD9, CAV1, KCNK3; Heritable, unknown | a. Systolic dysfunction | a. Chronic obstructive pulmonary disease | a. Hematological disorders: myeloproliferative disorders, splenectomy, chronic hemolytic anemia |
| b. Drugs and toxin-induced e.g fenfluramine | b. Diastolic dysfunction | b. Interstitial lung disease | b. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis |
| c. Associated with PAH: connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis | c. Valvular disease | c. Other pulmonary diseases with mixed restrictive and obstructive pattern | c. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 1” – Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis | d. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies | d. Sleep disordered breathing | d. Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH |
| 1”’ – Persistent PH of the newborn from serotonin reuptake inhibitors in pregnancy | e. Alveolar hypoventilation disorders | e. Alveolar hypoventilation disorders | |
| Prevalence | 68 – 78% in systolic heart failure, 85% in diastolic heart failure | 30 – 70% of COPD patients, 8 – 84% of ILD patients | 0.5 – 2% in survivors of acute pulmonary embolism | Unknown |

Table 1. Updated classification of pulmonary hypertension (updates from 2013 world symposium on pulmonary hypertension).
“back pressure”, mediated by right ventricular dysfunction [19-23] An example of this is acute on chronic Right-Ventricular (RV) dysfunction leading to increased kidney venous pressures and decreased effective kidney perfusion [24, 25]. Animal studies have demonstrated that an isolated increase in CVP leads to renal hypoperfusion and a decline in kidney function [20, 21]. Increased CVP leads to reduced trans-glomerular pressure gradients (through renal venous hypertension), and this triggers myogenic and neural reflexes, baroreceptor stimulation, activation of the Renin-Angiotensin-Aldosterone System, the sympathetic nervous system, and pro-inflammatory pathways, which are postulated to then lead to the decline in filtration fraction [25-27]. The activation of the Renin-Angiotensin-Aldosterone System and production of angiotensin-II, in particular, has been shown to activate NADPH oxidase, which generates superoxide, a reactive oxygen species that leads to progressive oxidative kidney injury [28-30]. Angiotensin-II also upregulates the inflammatory mediators, transforming growth factor-b, tumor necrosis factor-a, nuclear factor-kB, and interleukin-6 and stimulates fibroblasts, resulting in inflammation and fibrotic damage in the renal parenchyma [31, 32].

1.2. Effects of PH and AKI

Kidney injury that results from PH has been associated with an increase in mortality. In a study conducted by Mielniczuk et al. [33], 36% of the patients with AKI and PH died in the hospital compared with 5% in the PH group who did not develop AKI (OR for hospital death 13.3 ± 16, P = 0.03). Navaneethan et al. [34], showed that when the estimated GFR was examined as a continuous measure, a 5 mL/min/1.73m2 body surface area lower estimated GFR was associated with a 5% higher hazard for death. This increased risk of mortality was present irrespective of demographics, left-ventricular function, and PCWP [34].

Haddad et al., had interesting finds in patients with PAH who were hospitalized for acute right-side heart failure. The odds of developing AKI were higher among patients with chronic kidney disease, high central venous pressure, and tachycardia on admission. AKI was strongly associated with 30-day mortality after acute right-side heart failure hospitalization.

Gajanan D, et al. [19] showed that the group with high RA:PCWP ratio, a novel hemodynamic parameter reflecting right ventricular function, had a higher incidence of AKI, and this was associated with a higher 30-day (19.4% vs. 3.54%) and 90-day mortality (29% vs. 9.21%), respectively, compared with the low-ratio group. In other studies, high RA:PCWP has been shown to be a marker for increased all-cause mortality [35, 36]. In an analysis of the Cardiac Transplant Research Database (CTRD) over a span of 14 years, the RA:PCWP ratio was independently associated with an increased 2-year post cardiac transplant all-cause mortality [37]. Analysis from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial revealed that RA:PCWP was strongly correlated with worse baseline creatinine and poor outcomes at 6 months [38].

Again, the literature in this subject is very limited and offers a great opportunity for further research.

1.3. PH and CKD

Chronic Kidney Disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause [39]. Pulmonary Hypertension is closely associated with CKD. In an analysis of the Chronic Renal Insufficiency Cohort (CRIC) study population, the prevalence of pulmonary hypertension by echocardiography was 21% increasing proportionately with the degree of kidney dysfunction to as high as 32.8% with CKD stage 5 [40]. This reached 65% in dialysis patients [41]. Various factors including older age, anemia (hemoglobin, 10 g/dl), lower LVEF, and presence of LVH were independently associated with the presence of Pulmonary hypertension in CKD [40]. The most frequent type of pulmonary hypertension found among patients with CKD is group 2 pulmonary hypertension but up to 6-13% of patients may have concomitant pulmonary arterial hypertension or precapillary pulmonary hypertension [41]. The presence of pulmonary hypertension was independently associated with increased all-cause mortality and cardiovascular events among patients with CKD [40]. In turn, worsening renal function in patients with pulmonary hypertension independently predicted poor outcomes and mortality as well [42, 43]. This suggests a lot of crosstalk between these two distinct but closely related pathologies.

1.4. Pathophysiology of the Development of PH in CKD

Various mechanisms have been implicated in the pathophysiology of pulmonary hypertension in CKD. Chronic volume overload found among patients with LV dysfunction together with the increase in preload in patients with CKD, may induce pulmonary venous hypertension by both increasing pulmonary blood flow and adversely affecting LV function. In addition, myocardial stiffness secondary to chronic systemic hypertension and coronary artery disease, some frequent complication of CKD, may contribute to pulmonary hypertension [44]. Endothelial dysfunction in chronic kidney disease has also been implicated in the development of pulmonary hypertension with disturbances involving decreased nitric oxide and increased expression of endothelin resulting to increased pulmonary vascular resistance and subsequent pulmonary arterial hypertension [45-47]. CKD also induces a state of high PTH hormone levels with subsequent calcification of the vessels. These events contribute to the development of endovascular stiffness and endothelial dysfunction, which overtime accelerates the development of pulmonary hypertension [48-50]. A subset of patients with pulmonary hypertension progress to having “reactive” changes in their pulmonary vasculature and also develop high PVR as well as high PCWP [51]. Capillary and arterial remodeling develop from backward transmission of increased Left Atrial Pressure (LAP), challenging the vascular structural integrity and functional properties. Local activation of growth stimuli, such as angiotensin II, endothelin-1, and hypoxia, may contribute to this microvascular remodeling [52]. Presence of both high PCWP and elevated PVR (mixed PH) is associated with greater risk of death among patients with heart failure in comparison with Pulmonary Hypertension of elevated PCWP alone [53], no studies have addressed the direct effect of this reactive change of the pulmonary vasculature on kidney function so far (Fig. 1).
1.5. Pathophysiology of the Impact of PH on CKD

Pulmonary hypertension is in turn associated with chronic kidney disease or worsening renal function. Possible mechanisms include increased neuro-hormonal activation and right ventricular dysfunction [54]. Pulmonary hypertension is associated with a state of elevated catecholamine levels and activation of the renin angiotensin aldosterone system and is in turn associated with RV dysfunction and further worsening pulmonary hypertension [55-60]. In fact, animal studies showed that sympathetic denervation of the pulmonary artery improved hemodynamics and right ventricular function in pulmonary hypertension models [58, 59]. This excess neuro-hormonal activation contributes to kidney dysfunction as evidenced in animal models where angiotensin II infusion induced renal vascular remodeling [61, 62]. More compelling evidence further points out the role of excess neuro-hormonal activation in kidney dysfunction as shown by the efficacy of the use of RAAS blockers in delaying progression of renal dysfunction [63]. However, in an analysis of studies done in pulmonary hypertension, Schrier pointed out that activation of the RAAS system might come early in the course of pulmonary hypertension and levels might become normalized in late stages as cardiac output is returned to near normal state after compensatory sodium and water retention [64].

Another essential component in the pathophysiology linking pulmonary hypertension with chronic kidney disease is right ventricular dysfunction. The primary function of the right ventricle is to pump the systemic venous return into the pulmonary circulation [65]. As a result, RV is built to adapt better to an increase in preload than an increase in afterload [66]. Acute increases in pulmonary pressures such as in the setting of pulmonary embolism can lead to rapid elevations in RV afterload causing RV dilatation and disruption of the contractile apparatus and RV failure [67]. Meanwhile, chronic increases in RV afterload such as in pulmonary hypertension brought about by increased pulmonary vascular resistance may lead to RV remodeling and adaptation with eventual RV dysfunction and failure [67, 68]. Various mechanisms have been implicated in right ventricular remodeling including increased endothelin levels in animal studies of pulmonary hypertension and that use of endothelin antagonists promoted less RV fibrosis and hypertrophy [69]. Excess neuro-hormonal activation including increased sympathetic response and RAAS activation in the setting of adrenoreceptor downregulation, increased ANP and BNP levels, as well as increased activation of cytokines such as TNF, have all been associated with increased symptoms and poor outcomes in patients with RV dysfunction [31, 32, 55, 57, 60]. Right ventricular dysfunction in turn has long been implicated as a suspect in the progression of renal dysfunction in the setting of pulmonary hypertension. Right ventricular dysfunction can further decrease systemic cardiac output and hence renal perfusion by decreasing left ventricular preload through ventricular interdependence and pericardial constraint [64], resultant venous congestion can increase central venous pressure decreasing renal perfusion pressure via increased in back pressure [70-72]. Studies have shown that patients with pulmonary hypertension before kidney transplantation had more tendency for early graft dysfunction [73] and likewise reduced survival after kidney transplantation [74]. These data suggest that pulmonary hypertension either independently, or in association with right ventricular dysfunction, contributes to the progression of chronic kidney disease.

There is no definite answer as to the degree and predominant mechanism pulmonary hypertension affects kidney function.
1.6. Impact of PH in Patients with Left Ventricular Assist Devices (LVADS) on Kidney Function

The effect of markers of pre-operative RV dysfunction such as elevated CVP and low LV end-diastolic dimensions on perioperative acute kidney injury after LVAD placement is well documented. A recent post-market evaluation study showed right HF to occur in 9% of patients, representing 0.10 events per patient-year [77-85]. Left ventricular unloading by the LVAD may promptly increase venous return and overload the right ventricle resulting in RV overdistension and decrease myocardial perfusion, leading to RV failure. This, in turn, results in venous congestion to the kidneys, reducing perfusion and eGFR through the development of chronic type 2 cardio-renal syndrome [86]. However, despite the close interplay of pulmonary hypertension and the development of RVD, the impact of PH on overall patient and renal outcomes after LVAD placement remains unclear [87]. In a large single-center analysis of 227 patients that underwent continuous flow LVAD implantation, in patients with pre-operative high Pulmonary Vascular Resistance (PVR), a significant drop was noted post LVAD implantation [88]. High pre-operative PVR was associated with worse in hospital post-transplantation mortality, but no differences in survival were observed at 3 years in the groups with high and normal PVR. More data are needed to define the role of optimization of PH post LVAD on long-term kidney function.

1.7. PH in Hemodialysis Patients via Arterio-venous Access

There is a high prevalence of PH among patients with ESRD on chronic HD via a surgical A-V fistula. In view of the vasodilatory and antimitogenic properties of NO, it is possible that the attenuated basal and HD-induced NO production in patients with PH contributes to the increased pulmonary vascular tone. Furthermore, the partial restoration of normal PAP and CO in HD patients that underwent either temporal A-V shunt closure or successful transplantation indicates that excessive pulmonary blood flow is involved in the pathogenesis of the disease [89-101].

Yigla et al., recorded PAP and Cardiac-output (CO) values in 12 pre-dialysis patients without PHT a few months after the access formation, before treatment with HD was started, and the prevalence of PHT was calculated. The systolic PAP values were increased in 9 of the 12 pre-dialysis patients (42%) by 21+/−9 mm Hg to more than 35 mm Hg. Patients with and without PH differed only in that CO was significantly higher among the former. Pre-dialysis patients scheduled for access formation should be screened for the presence of sub-clinical PH. Positive patients should proceed to peritoneal dialysis or advance to kidney transplantation; rather than getting access and HD therapy [102].

2. EFFECT OF PULMONARY HYPERTENSION IN KIDNEY TRANSPLANTATION.

2.1. Pulmonary Hypertension and the Renal Allograft

Pulmonary hypertension is a significant co-morbidity in patients with End-Stage Kidney Disease (ESKD), with a reported prevalence varying from 18-56% in various observational studies [89]. PH is also an independent predictor of mortality in patients on maintenance dialysis, with the disease burden being several fold higher in patients on hemodialysis vs peritoneal dialysis [90, 91]. This section explores the impact of PH on kidney transplantation outcomes, and delineates the course of PH after kidney transplantation.

2.2. Impact of PH on Kidney Transplantation Outcomes

In a cohort of 215 kidney transplant recipients, Issa et al demonstrated that a pre-transplant right ventricular systolic pressures (RSVP) of greater than 50 mm Hg was independently associated with worse renal allograft outcomes [92]. This relationship was independent of other variables including older age, reduced left ventricular ejection fraction, low serum albumin, and delayed graft function. In addition, the hazard ratio for post-transplant death was 3.75 (P=0.016) with RSVP values of greater than 50 mm Hg, with dialysis vintage being the strongest correlate with RSVP severity. In another single institution experience, Zlotnick et al. demonstrated the association of PH with early renal allograft dysfunction in deceased donor allografts, but not in live donor allografts [93]. This association persisted beyond potential confounding recipient, donor and graft-based risk factors for early graft dysfunction. Pretransplantation PH (defined as RSVP> 35 mmHg) was independently associated with reduced renal allograft function in the first year of transplantation in another retrospective study of 206 recipients [94]. Worse outcomes with five-year renal allograft survival were reported in a single institution study in patients with pre-transplantation PH [95]. In this cohort of 638 transplant recipients, 209 patients had elevated PASP on pre-operative echocardiograms. Patients with PH prior to transplant had a lower graft survival rate at 5 years vs. patients without pulmonary hypertension (54.6% vs. 76.0%, p<0.05) and were nearly twice as likely to experience overall graft failure (crude HR 1.80, CI: 1.55, 2.08, adjusted HR 1.3, CI: 1.11, 1.51) during the study period.

In a large cohort of patients evaluated for potential kidney transplantation, advanced age, diabetes, reduced systolic function, pulmonary hypertension/RV dysfunction, regional wall motion abnormalities and listing status were associated with all-cause mortality [96]. Combined in a score where one point was given for the presence of each of the parameters
above, these factors were strongly predictive of increased mortality with a hazard ratio of 3.57, 6.80, and 44.47 for the presence of one, two, or more factors, respectively, compared with the absence of any of these factors.

In a single-center cohort consisted of 35 patients who underwent Simultaneous Heart-kidney Transplantation (SHKT) during 1996 to 2015, Delayed Graft Function (DGF) of the renal allograft occurred in 37% of patients, and pre-operative pulmonary hypertension was an independent risk factor for this. [97] There was a significant association between DGF and reduced median GFR at 1 and 3 years after transplant (p <0.005) in the same cohort, underscoring the impact of pre-operative PH on short and long-term renal allograft outcomes with simultaneous heart-kidney transplantation.

2.3. The Course of PH After Kidney Transplantation

Several small studies have demonstrated improvement in PH and allied parameters associated with PH such as LV systolic and diastolic function and blood pressure. A small case series described normalization of pulmonary systolic pressures post renal transplantation [93]. In a cohort of 425 kidney transplant recipients between 2001-2007, a significant reduction in PH was demonstrated post-transplant [98]. With the exception of BMI, the PASP had no significant correlation with any of the parameters analyzed including age, gender, hypertension, diabetes, smoking status, glomerular filtration rate, hemoglobin, hemodialysis duration, urine albumin and arterio-venous access. In a single-center analysis of 42 patients with pre and post-transplant echocardiograms, a significant reduction in systolic pulmonary arterial pressure was noted after renal transplantation [89]. In another retrospective experience, Casas-Aparicio et al showed a significant reduction in pulmonary arterial systolic pressure at 12 months after renal transplantation in 35 patients [99]. A significant improvement in ejection fraction and several LV parameters was also noted in this study.

2.4. Management of the Dual Burden of PH and CKD

The treatment of pulmonary hypertension in the setting of CKD is complex and has not been studied in depth. Since the majority of pulmonary hypertension in CKD is group 2 and in the absence of specific studies, if present, treatment for group 2 pulmonary hypertension in the general population can temporarily be used [44]. This includes treatment of the underlying heart disease which is commonly found in these patients [44, 76]. In patients with CKD, special attention to volume status should be made including the use of diuretics, following potassium levels, reducing dietary salt intake and appropriate dialysis treatment intensification [44, 77]. In dialysis patients with persisting pulmonary hypertension after correcting volume overload and optimizing ventricular function, right-sided cardiac catheterization and measurement of wedge pressure will determine the next step of treatment or to evaluate whether there is a need to address pulmonary arterial hypertension [44] as patients can present with combined pulmonary hypertension etiologies [76].

Meanwhile treatment of group 1 pulmonary hypertension remains the same, with vasoreactivity first assessed to see if patients respond to Calcium Channel Blockers (CCB) [78]. Other drugs shown to improve exercise tolerance and hemodynamics in a patient with group 1 pulmonary hypertension include endothelin receptor antagonists, PDE5 inhibitors, cGMP stimulator Riociguat, prostacyclin analogues and agonist selexipag, with macitentan, prostaglandin analogues and selexipag providing some morbidity and mortality benefit [78-83].

Adding to the complexity of treatment of patients with pulmonary hypertension and CKD includes the component of concomitant RV dysfunction. The use of digitalis in this setting should be closely monitored with digoxin levels, heart rate monitoring and ECG evaluation [77]. Targeting components of RV dysfunction can be done. Enhancing contractility with the use of inotropes such as dobutamine, correction of excessive RV preload such as using diuretics and avoiding volume loading, correcting reversible causes such as ischemia, hypotension, abnormal heart rhythms with cardioversion and appropriate use of vasopressors, and lastly, use of extracorporeal membrane oxygenation as appropriate [68, 84].

CONCLUSION

Pulmonary hypertension is not uncommon in patients with renal disease and vice versa; therefore, influences treatments and outcomes. The relationship is a complex phenomenon and multiple body systems and mechanisms are involved in its pathophysiology. Although the definition of pulmonary hypertension has evolved over time with the understanding of multiple interplays between the heart, lungs, kidneys, etc.; there is limited evidence to provide a specific treatment strategy when kidneys and lungs are affected at the same time. Nevertheless, available evidence appears to support new treatments and highlights the importance of individualized treatment. The new pulmonary hypertension classification system is more helpful in identifying therapeutic targets and offers a systematic approach to optimize the treatment as well as a management algorithm with a better understanding of the etiologies. It may eventually alter outcomes and enhance patient care and future investigations.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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