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Clinical Research

Predictors of Mortality after Surgery for Empyema Thoracis in Chronic Kidney Disease Patients

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Background: Surgical treatment of empyema thoracis in patients with chronic kidney disease is challenging, and few studies in the literature have evaluated this issue. In this study, we aim to report the surgical outcomes of empyema and to analyze factors predicting perioperative mortality in patients with chronic kidney disease.
Methods: This retrospective study included data from 34 patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2 for 3 or more months) who underwent surgery for empyema between 2012 and 2020. An analysis of demographic characteristics and perioperative variables, including complications, was carried out. Postoperative mortality was the primary outcome measure.
Results: Patients' age ranged from 20 to 74 years with a 29-to-5 male-female ratio. The majority (n=19, 55.9%) of patients were in end-stage renal disease (ESRD) requiring maintenance hemodialysis. The mean operative time was 304 minutes and the mean intraoperative blood loss was 562 mL. Postoperative morbidity was observed in 70.5% of patients (n=24). In the subgroup analysis, higher values for operative time, blood loss, intensive care unit stay, and complications were found in ESRD patients. The mortality rate was 38.2% (n=13). In the univariate and multivariate analyses, poor performance status (Eastern Cooperative Oncology Group >2) (p=0.03), ESRD (p=0.02), and late referral (>8 weeks) (p<0.001) significantly affected mortality.
Conclusion: ESRD, late referral, and poor functional status were poor prognostic factors predicting postoperative mortality. The decision of surgery should be cautiously assessed given the very high risk of perioperative morbidity and mortality in these patients.

Keywords: Chronic kidney failure, Empyema thoracis, Surgery, Mortality, Patient outcome assessment

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or decreased kidney function for 3 or more months, irrespective of the cause [1]. Patients with CKD are more susceptible to the development of pleural effusion [2,3]. Causes of pleural effusion include bacterial infections, tuberculosis, volume overload, uremic pleuritis, and malignancy. Inappropriately treated pleural effusion, if infected, develops into empyema. The underlying mechanisms for a higher risk of infection include multiple attempts at aspiration, altered immunity, poor nutritional status, multiple other comorbid conditions, and susceptibility to nosocomial and dialysis catheter-related infections [4]. In this group of patients, empyema poses a significant risk of morbidity and mortality [5].

Surgery is the treatment of choice for chronic empyema. However, surgical intervention in this group of patients is a therapeutic challenge for several reasons. Patients with CKD are more susceptible to various metabolic and hemodynamic changes in the perioperative period such as electrolyte disturbances (hyperkalemia), unexpected hemodynamic alterations, and propensity for postoperative bleeding [6,7]. Studies reporting surgical experiences for empyema in patients with CKD are sparse in the literature. Herein, we present the outcomes of surgery for empyema

in CKD patients and analyze various factors influencing mortality.

Methods

Study design and patients

This is a retrospective analysis of prospectively maintained data from 34 CKD patients who underwent decortication for empyema thoracis between March 2012 to February 2020 at a thoracic surgery center in New Delhi, India. This study was approved by the Institutional Review Board of Sir Ganga Ram Hospital (IRB approval no., Ethic/SGRH/204). Informed consent was obtained from all individual participants included in the study.

Preoperative evaluation

Demographic details, duration of kidney disease, duration of hemodialysis (if applicable), radiological reports, and previous interventions were recorded. Computed tomography of the chest was performed in all patients to assess the disease state. Trapped lung, multi-loculated collection, and incompletely drained infected pleural collection even after tube thoracostomy were considered to be indications for surgical intervention.

All patients had a detailed preoperative cardiac and nephrology workup. Adequate nutritional preparation and physiotherapy counseling were done. Electrolyte abnormalities were corrected in accordance with the attending nephrologist's opinion. For post-renal transplant patients, immunosuppressive medications were stopped or their dosages modified in accordance with the advice of the transplant physician. All patients with end-stage renal disease (ESRD) underwent hemodialysis 1 day prior or on the day of surgery. Patients were infused with 20% human albumin and/or various blood components to address low albumin levels, low hemoglobin, low platelet count, or elevated prothrombin time/international normalized ratio. All possible nephrotoxic medications were avoided during the hospital stay.

Surgical details

All surgical procedures were performed with the patient under general anesthesia in the lateral decubitus position, with single lung-ventilation achieved with a double-lumen endotracheal tube. The procedures performed included video-assisted thoracoscopic surgery (VATS) or open debridement or decortication. All pus locations were broken and debridement of the cavity was done. Pressure packing of all oozing surfaces should be done to minimize blood loss. This was followed by complete visceral and parietal decortication. Lung expansion was checked, and any sites of major air leak were assessed and corrected. Hemostasis was ensured with a combination of pressure packing, electrocautery, and argon plasma coagulation. Two chest drains were placed and connected to a Thopaz digital negative-suction device (Medela, Baar, Switzerland) with a negative pressure of 20 cmH_2O. According to protocol, all patients were transferred to the intensive care unit (ICU) in an intubated state and monitored for urine output, chest tube drainage, blood pressure fluctuations, and other vital signs. Blood gas analysis was carried out every 6 hours. Once the patient was hemodynamically stable, the decision of extubation was made. For patients who were on maintenance hemodialysis before the surgery, hemodialysis (without heparin) was done on the first postoperative day and then the patient was extubated. Patients were transferred to a high-dependency unit for further observation and then transferred to the ward once stabilized.

Postoperative care and follow-up

Supervised chest physiotherapy was continued after surgery to maintain good lung expansion. Special attention was paid to adequate nutritional intake and patients unable to consume enough nutrients orally were administered an appropriate diet through a nasogastric tube. Antibiotics were modified based on intraoperative cultures. Chest drains were removed when there was no air leak, and when the drainage was non-purulent/hemorrhagic and was less than 100 mL in 24 hours. Patients were discharged from the hospital either after drain removal or with drains if they had prolonged drainage or air leak. Duration of the postoperative air leak, duration of the chest tube, hospital stay, wound infection, recurrence of disease, and mortality during the hospital stay were monitored and recorded. After discharge, patients were monitored for the status of lung expansion and any other complications. Follow-up was done at the outpatient clinic, first 1 week after discharge, and every month thereafter for 6 months. All patients had a chest X-ray every month until 6 months to assess the status of lung expansion and any recurrence of the collection.

Statistical analysis

Continuous variables are presented as mean±standard

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deviation or median with interquartile range. Categorical variables are expressed as frequencies and percentages. Normally distributed continuous variables were compared between the groups using the Student t-test. Nominal categorical data between the groups were compared using the chi-square test or Fisher exact test as appropriate. Non-normally distributed continuous variables were compared using the Mann-Whitney U-test. Multivariate analysis was done using a step-wise binary logistic regression model. For all statistical tests, a p-value of less than 0.05 was taken to indicate a significant difference. Statistical testing was conducted with IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA).

Definitions used

"CKD III" is defined as the estimated glomerular filtration rate (EGFR) of 30–59 mL/min/1.73 m^2 with no requirement of hemodialysis [8]. "CKD IV" is defined as the EGFR of 15–29 mL/min/1.73 m^2 with no requirement of hemodialysis [8]. "ESRD" is defined as EGFR of <15 mL/min/1.73 m^2 with the requirement of dialysis to maintain body homeostasis [8]. "Maintenance hemodialysis" is defined as patient undergoing regular hemodialysis for more than 3 months. "Perioperative mortality" is defined as death due to any cause within 90 days of surgical intervention.

Results

Demographic characteristics and surgical procedures

There were 29 men (85.2%) and 5 women (14.8%), with a mean age of 56.6 years (range, 20–74 years). Hypertension (79.4%) was the most common associated comorbidity, followed by diabetes (44.1%). Seventy-six percent of patients were referred more than 4 weeks after the onset of disease. All of the patients had undergone preoperative aspiration at least once before being referred to us. All patients had a chronic disease. In our study group, 58.9% of patients developed para-pneumonic empyema, and 41.1% of patients developed para-pneumonic effusion/empyema with the further complication of infected clotted hemothorax due to multiple aspirations. The majority (n=19, 55.9%) of patients had ESRD and were on hemodialysis, followed by those with CKD III and IV (n=9, 26.5%) and renal allograft recipients (n=6, 17.6%) (Table 1).

Table 1. Demographic and clinical characteristics of the patients

Characteristic	Value
Sex	
Male	29 (85.2)
Female	5 (14.8)
Mean age (yr)	56.6 (20–74)
Co-morbidities	
Hypertension	27 (79.4)
Diabetes mellitus	15 (44.1)
Coronary artery disease	7 (20.6)
Pulmonary emphysema	4 (11.8)
Hypothyroidism	3 (8.8)
Hepatitis B positive	2 (5.8)
Hepatitis C positive	2 (5.8)
Symptomatology	
Dyspnea on exertion	34 (100)
Fever	28 (82.3)
Chest pain	19 (55.9)
Cough with expectoration	18 (52.9)
Time of referral (wk)	
<4	8 (23.5)
4–8	8 (23.5)
>8	18 (53)
Spectrum	
PPE	20 (58.9)
PPE complicated with infected clotted hemothorax	14 (41.1)
Side of disease	
Right side	22 (64.7)
Left side	12 (35.3)
Preoperative interventions	
Aspiration	34 (100)
Intercostal drain placement	19 (55.9)
Type of renal dysfunction	
End-stage renal disease (CKD-V) on maintenance hemodialysis	19 (55.9)
CKD III, IV not on hemodialysis	9 (26.5)
Renal allograft recipient status	6 (17.6)

Values are presented as number (%) or mean (range).
PPE, para-pneumonic empyema; CKD, chronic kidney disease.

Perioperative surgical outcomes

Perioperative variables are described in Table 2. In our initial cases, we opted for the VATS decortication method. The procedure was started by VATS in 9 patients and was completed by this approach in 7 patients. Two patients required conversion to the open method because of uncontrolled diffuse oozing/bleeding faced intraoperatively. However, after these initial 9 cases, we switched to posterolateral thoracotomy as our routine surgical approach because of the high morbidity and mortality we experienced with the VATS approach. Overall, the mean operative time was 304±68 minutes, and mean intraoperative blood loss

Table 2. Comparison of perioperative variables in the 3 groups of patients

Characteristic	ESRD (n=19)	CKD (n=9)	Post-RAR (n=6)	p-value
Operative time (min)	324±58	289±51	285±51	<0.001
Blood loss (mL)	601±59	506±68	528±55	<0.001
Method of surgery				
Open	11	9	5	
VATS	9	0	0	
Conversions from VATS	2	0	0	
Mean intensive care unit stay (day)	12.3±7.4	5.8±4.3	6.4±5.4	<0.001
Pus/peel culture positivity	14	5	4	0.63
Intercostal drain duration (day)	14.8±10.9	9.5±7.9	8.8±8.1	<0.001
Complications (overall)	16 (47)	4 (11.7)	4 (11.7)	0.40
Bleeding	3	0	1	
Re-collection	5	0	0	
Wound infection	5	1	3	
Prolonged air leak (>7 day)	9	4	3	
Cardiac arrythmias	2	1	1	
Hospital stay (day)	19.4±18.3	13.1±10.4	16.6±11.7	0.07
<90-day mortality	10	1	2	0.10

Values are presented as mean±standard deviation, number, or number (%).
ESRD, end-stage renal disease; CKD, chronic kidney disease; RAR, renal allograft recipient.

was 562±86 mL. In comparisons of individual groups, operative time, intraoperative blood loss, mean ICU stay, and the duration of the intercostal drain (ICD) showed higher values in ESRD patients than in the CKD III, CKD IV, and post–renal allograft recipient groups.

Complications

Postoperative complications occurred in 24 patients (70.5%). Prolonged air leak was the most common complication (47%), followed by wound infection, recollection, bleeding, and cardiac arrhythmias. In cases with prolonged air leak, the ICD was kept connected to underwater-seal drainage for a maximum of 4 weeks. After this, the ICD was disconnected from the underwater seal bottle and kept on open drainage for 24 hours. If there was no lung collapse shown on a chest X-ray examination, the chest tube was removed despite active air leak. Wound infection was managed with thorough debridement and vacuum-assisted closure. Re-collection occurred in 5 patients (14.7%), of whom 3 patients were managed with reinsertion of ICD and prolonged antibiotics, whereas 2 patients finally required window thoracostomy. Four patients (11.7%) developed atrial fibrillation, which was managed with Injectable amiodarone therapy. Postoperative bleeding occurred in 4 patients (11.7%), all of whom required repeated surgery and evacuation of the hematoma. In the individual group analysis, ESRD patients had significantly higher operative times, intraoperative blood loss, ICU stay, and ICD duration. ESRD patients also had higher rates of total complications, including postoperative air leak, recollections, and bleeding, than the other 2 groups (Table 2).

Out of the 34 patients in the study population, 23 had positive culture results, while the other 11 were culture-negative. The causative micro-organisms in those 23 patients were *Pseudomonas aeruginosa* in 10, *Klebsiella pneumoniae* in 7, *Enterococcus faecium* in 5, and *Staphylococcus epidermidis* in 1. However, culture positivity did not significantly affect mortality.

Details of mortality and factors influencing mortality

In total, 13 deaths occurred in the study group, corresponding to a mortality rate of 38.2%. Mortality was significantly higher in the ESRD group than in the other 2 groups (n=10, p=0.02). In the univariate analysis, poor performance status (Eastern Cooperative Oncology Group >2) (p=0.03), ESRD (p=0.02), late referral (>8 weeks) (p<0.001), and preoperative serum creatinine >8 mg/dL (p=0.03) were significantly associated with mortality. In the multivariate analysis, all of the above factors except serum creatinine levels were also found to be poor prognostic factors predicting mortality. Septic shock was the major cause of mortality, followed by bleeding (Table 3). Nearly 46% of all deaths happened in the first 9 cases in the first 2 years of

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Table 3. Analysis of factors affecting mortality

Variable	No. of patients	Mortality	Univariate analysis		Multivariate analysis	
			OR	p-value	OR	p-value
Age of patient (yr)			1.3	0.42	-	-
≤40	6	2				
>40	27	11				
ECOG Performance Scale			9.5	**0.03**	8.1	**<0.001**
≤2	14	1				
>2	20	12				
Type of renal dysfunction			6.1	**0.02**	4.9	**0.04**
ESRD on MHD	19	10				
CKD III, IV	9	1				
RAR status	6	2				
Duration of symptoms (wk)			21.1	**<0.001**	19.2	**<0.001**
<8	16	0				
≥8	18	13				
Preoperative serum creatinine (mg/dL)			5.6	**0.03**	3.1	0.11
≤8	19	4				
>8	15	9				
Culture positivity			1.2	0.71	-	-
No	11	5				
Yes	23	8				

Bold font indicates the values which were statistically significant (p<0.05).
OR, odds ratio; ECOG, Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; MHD, maintenance hemodialysis; CKD, chronic kidney disease; RAR, renal allograft recipient.

Table 4. Evaluation of surgical experience over time

Variable	March 2012 to February 2014	March 2014 to February 2016	March 2016 to February 2018	March 2018 to February 2020	p-value
No. of cases	9	7	11	7	
Open	0	7	11	7	
VATS	9	0	0	0	
Mortality	6 (66.7)	2 (28.5)	3 (27.2)	2 (28.5)	0.24
Cause for mortality					
Sepsis	4	2	3	1	
Bleeding	2	-	-	1	

Values are presented as number or number (%).
VATS, video-assisted thoracoscopic surgery.

our experience (March 2012 to February 2014). Thereafter, based on an analysis of the causes of death, we modified our surgical protocols, and in the last 6 years (March 2014 to March 2020), the mortality rate decreased to nearly 28% (Table 4).

Discussion

Surgical management of empyema in CKD patients poses a significant challenge to the surgeon as well as the patient because of the high rate of perioperative morbidity and mortality [9]. Patients with CKD and ESRD are more susceptible to various infections including empyema thoracis due to their immunosuppressed status [10-13]. Patients with CKD and ESRD are also affected by complex hematological abnormalities such as anemia, thrombocytopenia, and altered leukocyte function [14]. The decrement in the number of platelets, abnormal platelet-vessel wall interactions, and platelet dysfunction predispose CKD patients to bleeding diathesis [15]. This may be the reason why 41% of our patients presented with clotted hemothorax secondary to multiple failed attempts of pleural aspiration.

In ideal situations, the decision of surgical intervention

should be taken within a few days after initial intercostal drainage. However, empyema patients most often undergo a staged procedure, which includes prolonged antibiotics, multiple rounds of aspiration, and intercostal drainage [16]. Often, this staged approach leads to unwarranted delays in the definitive treatment process and causes prolongation of the infective process. This predisposes the patients to more postoperative morbidity and mortality because of deteriorated nutritional status, as well as further worsening of hemoglobin levels and serum albumin levels causing deterioration in patients' performance status. All these factors are often present together in most patients [17]. In our study population, more than 75% of patients were referred more than 1 month after diagnosis for surgical intervention. Late referral (>8 weeks) and poor performance status were strong predictive factors for postoperative mortality ($p< 0.0001$).

The outcome of surgery also depends on the stage of CKD. ESRD patients on chronic dialysis usually have a wide range of metabolic and hemodynamic changes and weaker immunity [18]. Therefore, patients on hemodialysis are at a high risk of postoperative issues such as a tendency for bleeding, poor wound healing, higher infection rates, electrolyte disturbances, and hemodynamic instability [19]. The presence of associated comorbid conditions also poses increased difficulties and makes empyema management even more complicated. In our study, we similarly observed that ESRD patients on regular dialysis had higher rates of postoperative complications and prolonged hospital stay, as well as significantly higher mortality than CKD III and IV patients. Of the 6 patients who were renal allograft recipients, 2 patients died. Both of these patients had graft rejection for which they were undergoing maintenance hemodialysis. Chronic immunosuppression in renal allograft recipients due to immunosuppressive medications often predisposes these patients to postoperative infections.

Meticulous intraoperative management is essential to prevent further kidney damage [20]. There should be a rapid return to the previous dialysis schedule to optimize the physiological status of patients already on maintenance hemodialysis. All CKD patients with empyema thoracis were kept electively intubated with slightly higher positive end-expiratory pressure the first postoperative day, following our standard protocol. We believe that the possibility of immediate postoperative bleeding/oozing decreases due to tamponade by the completely expanded lungs. VATS is usually the preferred modality in CKD patients, as its minimal invasiveness reduces the inflammatory and cytokine response after surgery [21-23]. In our initial cases, the VATS method was used for decortication. However, continuous diffuse oozing from the chest wall after parietal pleurectomy was found to be very difficult to control with the VATS approach. The surgical duration of VATS decortication was also longer than that of open decortication. For these reasons, we made the conscious decision to perform open decortication in all patients with CKD, despite our extensive experience in managing stage III empyema through the VATS approach [16]. A few reports have highlighted the usability of VATS in such patients, albeit with higher reoperation rates (34.8%) [24]. We had an overall 38.2% mortality rate in our study group. Around 46% of the instances of mortality occurred in the first 2 years, where we struggled to formulate and standardize the surgical protocols for this difficult group of patients. We were subsequently able to reduce the mortality rate to 28%, which is similar to that reported in a previous surgical series [24]. This reduction was made possible by careful patient selection and standardization of the operative approach, intraoperative anesthetic management, and postoperative protocols. In the first 2 years of our experience, all patients who were operated were ESRD patients who were referred late, in a very moribund state with an altered coagulation profile. We initially managed all such patients with VATS approach. This approach usually led to longer operative times and higher blood loss, thus causing more intraoperative hemodynamic alterations, which increased the risk of mortality.

The major change in our approach after this experience was to perform surgery by thoracotomy, following the principle of "quick going in–quick coming out," with better control over hemostasis. Several extra measures taken to achieve reduced intraoperative blood loss, including pressure packing of oozing surfaces with sponges, routine use of an argon plasma coagulator to coagulate the oozing areas, and an intravenous injection of 1 g of tranexamic acid before starting parietal pleurectomy. In addition, only a few experienced anesthesiologists handled anesthesia in these patients, with strict maintenance of the mean blood pressure above 70–80 mm Hg intraoperatively. The protocols in the postoperative phase included resumption of hemodialysis as soon as possible, avoiding excess fluid replacement, early resumption of oral fluids and diet, early ambulation with aggressive chest physiotherapy, and routine application of a digital negative-suction device to the chest tubes. Adequate postoperative analgesia was achieved with injectable paracetamol and the dosage of pain relief measures was titrated according to the requirements of each patient.

Limitations

The retrospective nature of this study is one of its major limitations. The second most significant limitation is the heterogeneity of the cohort that was studied. The patients ranged from non-dialysis-dependent patients to previous allograft recipients on immunosuppression. Third, the policy of surgical management was modified over time (VATS to open) and was not standardized throughout the procedure. Another potential limitation of this study is the lack of a control group (i.e., patients managed by non-surgical methods). This is likely to have caused several biases, including selection, detection, and performance bias. Finally, the power of this study was also limited by the analysis of a very small cohort of patients, which may also call into question the credibility of multivariate analysis used to assess factors affecting mortality. Further randomized studies with a greater number of patients and standardized treatment protocols are required further to assess these findings.

Conclusion

Surgical management of empyema thoracis in patients with CKD is a therapeutic challenge. Proper identification and addressing of modifiable risk factors in the preoperative period, meticulous intraoperative techniques, and vigilant postoperative management are mandatory, as these patients are prone to a very high risk of perioperative morbidity and mortality. ESRD, late referral, and poor performance status were poor prognostic factors predicting postoperative mortality. Therefore, based on these risk factors, the decision to perform surgery should be carefully weighed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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