Original Research Article

Risk of bleeding in patients with chronic kidney disease undergoing bronchoscopy

Abstract

Background:

Complications rates from bronchoscopy are low, however chronic kidney disease (CKD) is considered a risk factor for procedural bleeding. The aim of the study is to evaluate bleeding complications CKD patients undergoing bronchoscopy with either transbronchial (TBLB), endobronchial biopsies (EBBX), Endobronchial Ultrasound transbronchial needle aspiration (EBUS-TBNA) and/or brushings.

Methods:

Retrospective analysis of patients with Chronic kidney disease who underwent bronchoscopy with biopsy, brushings and/or transbronchial needle aspiration from 2012 to 2019. Patients were grouped in 5 groups based on the National Kidney Foundation clinical guidelines. Bleeding was categorized as mild, moderate, and severe bleeding.

Results:

894 patients were identified; bleeding complications were seen in 103 (11.5%) patients. Mild bleeding in 51 (5.7%), moderate bleeding in 46 (5.1%) and severe bleeding in 6 (0.67%) cases. No association between CKD subgroups and bleeding complications. There were no differences in number of biopsies or passes done in CKD groups. 790 (88%) patients underwent TBLB followed by brushing in 329 (36.8%), EBBX in 300 (33.5%) and EBUS-TBNA in 290 (32.4%). Majority of bleeding complications occurred in patients undergoing TBLB. Patients with serum creatinine of 2 mg/dL or higher vs 3 mg/dL had no statistical difference for bleeding complication.

Conclusion:

There is no correlation in bleeding complications in patients with CKD undergoing Bronchoscopic biopsies. Most of complications were mild or moderate and did not required major interventions; risk of severe bleeding remains low, in those patients. There is no correlation between CKD stage or use of empirical serum creatinine cut off and risk of bleeding. Bronchoscopy remains a safe procedure in patients with CKD.

Introduction:

Flexible fiberoptic bronchoscopy (FFB) is a valuable tool for the diagnosis of pulmonary disorders that is considered safe and effective procedure.The evaluation of the airways in bodies has been described throughout medical history since before Hippocrates. Gustav Killian who removed a pork bone from a farmers airway in 1976 is generally considered the father of Bronchoscopy.In 1967 Shigeto Ikeda invented the fibreoptic bronchoscopy that revolutionized the field.In the last twenty years we have seen an exponential increase in the type of bronchoscopic procedures performed to improve the diagnostic yield and minimize more invasive procedures. Endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA) is one of the most important additions to the armamentarium. The two major feared complications of FFB are hemorrhage and pneumothorax usually associated with transbronchial biopsies (TBLX) and less with brushing, endobronchial biopsies (EBBX) or EBUS-TBNA. The incidence of bleeding complications by various studies in the US and worldwide is low [1,2]. Quantification of exact bleeding is difficult as the blood is mix with saline or aspirated fluid. In general, classification based in the type of clinical intervention necessary to stop the bleeding and stabilize the patient has been used for better reporting and comparison of studies. The incidence of massive bleeding after bronchoscopy is as small as 0.15% [3] to as high as 45% following TBLB in uremic patients [4,5]. A serum creatinine level of 3 mg/dL or higher, or a serum urea level of 30 mg/dL or greater is considered a relative contraindication to TBLB [6,7,8].

A bleeding incidence of 11% has been reported in patients with risk factors for bleeding especially with coagulopathy [7].There are no large or current studies focusing in

bleeding complications in patients with chronic kidney disease (CKD) undergoing TBLB, EBBX, brushing and/or EBUS-TBNA.

The aim of the study was to evaluate bleeding complications in patients with CKD undergoing FFB with any procedure like TBLB, EBBX, brushings and/or EBUS-TBNA.

Material and Methods:

Study design and patients:

This was a retrospective analysis of all adult patients who underwent bronchoscopy with biopsy (TBLB, EBBX), brushings and/or EBUS-TBNA at our institution. The study period was January 2012 to August 2019. Inclusion criteria: patients with CKD who underwent bronchoscopy with any or a combination of bronchopic procedure of TBBX, EBBX, brushing or EBUS-TBNA.

Exclusion criteria:a) patients with acute kidney injury, b) patients where the indication for bronchoscopy was evaluation of hemoptysis c) none of above bronchoscopic procedures were performed d) Pediatric patients < 18 years of age.

Ethics approval: This study protocol adhered to the amended Declaration of Helsinki and was approved by our Institutional Review Board (approval number 11101602). As this is a retrospective data abstraction from electronic medical records, informed consent was waived.

Our institution is a community teaching hospital with ACGME accredited pulmonary fellowship training. We have 9 pulmonary and critical care faculty and 6 fellows (3 first year and 3 second year fellows). A standard pre procedure safety check list including clinical and laboratory information as well as medications and planned procedures is used. The endoscopy suite is staffed by anesthesiology responsible for sedation, bronchoscopy nurse, a patient care technician, pulmonary fellow in training (either first or second year) and a faculty member supervising the bronchoscopy. In the first 3 months of training a senior fellow is present to assist the junior fellow and take over bronchoscopy if necessary.

Bronchoscopies were performed using a standard flexible bronchoscope (Olympus America Inc; Melville, NY). All bronchoscopies were performed under local anesthesia with conscious sedation in bronchoscopy suite or under general anesthesia in the operating room based on preoperative risk assessment. All EBUS-TBNA and high-risk bronchoscopies were performed in the operating room under general anesthesia as per division protocol. Bronchoscopies were performed by a pulmonary fellow and a faculty. Faculty are present for the entire duration of the procedure and assists in all planned procedures including biopsy. Transbronchial biopsies were all guided by fluoroscopy.

Methods to minimize or control bleeding:

Faculty use either a proximal view approach or wedge approach depending on their personal preference. During the withdrawal of the forceps, if significant bleeding is encountered, the bronchoscope is maintained in the wedged position (Wedge approach) or positioned to wedge position (proximal view approach) in the segment or subsegment. If bleeding persists or fails to diminish, we maintain the wedge position for a prolonged period to allow thrombus formation. We use instillation of 10–15mL of iced saline or dilute epinephrine (1 cc in 10 ml of saline) through the bronchoscope into the bleeding area for several seconds to help stem bleeding. We withdraw the scope when we no longer see stream of blood after instillation of saline. If bleeding persist then advanced bronchoscopic techniques are used (bronchus blocker or catheter, or use of fibrin sealant)

Data abstraction:

All data including demographic, clinical information and details regarding medications and bronchoscopic procedures were retrospectively extracted from medical records.

Definition of Bleeding during bronchoscopy

It is difficult for research and comparison purpose to accurately sub classify bleeding during FFB into minor, moderate or severe based only on an estimated or measured volume of blood loss during the procedure. We classified severity of bleeding using the

suggested classification of other researchers based in the intervention used to manage bleeding (9).

Classification:

No bleeding:

No intervention needed; no blood suctioned continuously. Bleeding stops spontaneously.

Mild bleeding:

Continued suctioning of blood from the airways.

Bleeding stops spontaneously.

Moderate bleeding:

Intubation of the biopsied segment with the bronchoscope

into the wedge position.

Use of adrenaline or cold saline to stop bleeding.

Severe bleeding:

Placement of bronchus blocker or catheter, applying fibrinsealant

Resuscitation, blood transfusion, admission to critical care unitor death

Definition of Chronic Kidney Disease:

Chronic kidney disease is defined as kidney disease of duration of more than 3 months. All patients had serum creatinine values (mg/dL) obtained within 48 hours prior to FFB. Patients were grouped in 5 groups based on the National Kidney Foundation clinical guidelines (10) as follows:

Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m 2)

Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m 2)

Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m 2)

Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m 2)

Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m 2 or dialysis)

Statistical analysis:

Statistical software SPSS was used for analyses. For discrete variables, Chi-square test was used. If those coefficients are close to zero, there is no relationship. Between 0,1 – 0,2, relationship is weak. From 0,2 to 0,3 – it means moderate relationship and 0,3 and higher indicates strong relationship. In case of continuous variables, ANOVA – analysis of variance was used. It verifies whether the value of one variable has a statistically significant effect on the value of a different variable for given groups. If the p-value is less than 0.05, the null hypothesis was rejected. ANOVA will only find out if the values differ between all groups, not specifically, between which two groups they differ. Student's two-sample unpaired t-test was used for this. It compares the mean value μ1 of one group with the mean value μ2 of the other group. Logistic regression was performed between dependent variable and independent variables to predict variables that predicted bleeding. If p-value is larger than 0.05, it means that this variable is not statistically significant and there is no causal relationship.

Results:

We identified 894 patients with CKD who underwent bronchoscopy with any of following procedures: TBLB, EBBX, brushing and/or EBUS-TBNA. Most of the patients in the cohort were males, (51.5%) and smokers (63.5%). Patients with stage 3 CKD were older compared with any of the other groups. Comorbid conditions were presents in around 30% of the group with patients with CKD stage 5 (ESRD) more likely to have heart failure and pulmonary hypertension, see Table 1.

Table 1: Demographics and comorbid conditions

Demographics	CKD 1 n=368 (41%)	CKD 2 n=300 (34%)	CKD 3 n=172 (19%)	CKD 4 n=32 (4%)	CKD 5 n=22 (2 %)
Age, yr	52.9	58.3	61.8	60.1	53.1
Gender, No (%)					
Female	214 (58%)	122(41%)	79(46%)	10(31%)	9(41%)
Male	154 (42%)	178 (59%)	93 (54%)	22 (69 %)	13 (59%)

Race Black Hispanic Other	175 (48%) 117 (32%) 76 (20%)	122 (41%) 105 (33%) 70 (26%)	69 (40%) 64 (37%) 39 (23%)	9 (28%) 9 (28%) 14 (44%)	11(50%) 6 (27%) 5 (23%)
Tobacco use	224 (60%)	206 (68%)	103 (59%)	21 (65%)	14 (63%)
Body Mass Index	26.1	26.7	27.3	26.4	25.0
Comorbid conditions					
HIV Positive	112(27%)	97 (32%)	64 (36%)	9 (28%)	8 (36%)
Malignancy	63 (17%)	54 (18%)	34 (19%)	4 (12%)	4 (18%)
Liver Cirrhosis	8 (2%)	11(3.6%)	6 (3.4%)	2 (6%)	0 (0%)
Hepatitis C and/or Hepatitis B	57 (15%)	44 (14%)	32 (18%)	8 (25%)	3 (13%)
Heart failure	24 (6%)	18 (6%)	17 (9%)	5 (15%)	5 (22%)
Pulmonary Hypertension	94 (25%)	92 (30%)	55 (31%)	11 (34%)	13 (59%)

Comparison of procedures based on creatinine levels are shown in Table 2. 534 (60%) of these procedures were performed under conscious sedation and 360 (40%) were performed in Operating room under General anesthesia (GA). Of the 360 patients undergoing procedure under GA, 334 patients has creatinine levels less than 2 mg/dL ,14 had creatinine Between 2mg/dL and 3mg/dL and 12 patients had creatinine over 3 mg/dL .

Comparison of risk factors for bleeding is shown in table 2. Despite platelets count to be within normal range, we found a statistically difference between each group (p = 0.0078). Close to half of patients with stage 4 and 5 CKD were taking aspirin, few patients were on chronic clopidogrel or other anticoagulants, which were discontinued prior to FFB as per bronchoscopy policy and protocols of the division. Pulmonary hypertension for purpose of this study was defined as a right ventricular systolic pressure (RVSP) or 40 mmHg or higher. Patients with CKD stage 4 and 5 had higher RVSP (p = < 0.001), see Table 2.

Table 2: Select Variables associated with bleeding.

Variable	CKD 1 n=368	CKD 2 n=300	CKD 3 n=172	CKD 4 n=32	CKD 5 n=22	p-value
INR	1.42	1.15	1.70	1.10	1.23	0.39
PTT	31.6	31.4	31.9	33.4	32.4	0.4
Platelets	272	261	233	239	258	< 0.001
On aspirin *	66	65	59	13	10	0
On clopidogrel*	3	8	6	1	1	0.22
On any anticoagulation*	19	17	6	0	2	0.46
Echocardiogram: Pulmonary HTN (RVSP ≥ 40mmHg)	121	128	81	15	16	<0.001

- *Aspirin, Clopidogrel and anticoagulation were discontinued before bronchoscopic procedure as per policy and protocols of the Pulmonary and Critical care division.

There were no differences in pre bronchoscopy interventions to minimize the risk of bleeding during the procedure. Desmopressin was used as per bronchoscopist decision; 22 (0.2%) of the 894 patients received it. All patients with end-stage renal disease (ESRD) were receiving hemodialysis, in 14 of them dialysis was done 24 hours prior to bronchoscopy. Majority of the bronchoscopies were performed under conscious sedation (59.7%). There was no difference between CKD stage and type of sedation used for bronchoscopy (p=0.29)

Bleeding complications were seen in 103 (11.5%) patients, mild bleeding in 51 (5.7%) followed by moderate bleeding in 46 (5.1%) cases who required local epinephrine or cold saline administration and severe bleeding in 6 (0.67%). No patient required mechanical ventilation or use of airway blocker to control bleeding; there was no bleeding associated death either. There was no association between CKD groups and bleeding complications (*p*=0.81).

Evaluation of the type of bronchoscopic procedures done revealed that 790 (88%) patients underwent TBLB followed by brushing in 329 (36.8%), EBBX in 300 (33.5%) and

EBUS-TBNA in 290 (32.4%). We found no differences in the type of bronchoscopic procedures performed(p=NS), number of TBLB or EBUS-TBNA passes and stage of CKD. Majority of bleeding complications occurred in patients undergoing TBLB. Table 3

Table 3: Comparison of bronchoscopic procedures and bleeding severity in patients with chronic kidney disease

Type of Bronchoscopic Procedures	Bleeding Severity *(Ref 9)			Severity of Chronic Kidney Disease * (Ref 10)					Total number bleeding
	Mild	Moderate	Severe	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5	
Total bronchoscopies (894)	51 (5.7%)	46 (5.1%)	6 (0.6%)	39 (10%)	34 (11%)	22 (12%)	4 (12%)	4 (18%)	103 (100%)
TBLB (280)	16 (5.7%)	19 (6.7%)	2 (0.7%)	115 (41 %)	95 (33.9%)	50 (17.8%)	11 (3.9%)	9 (3.2%)	37 (35.9%)
TBLB + Brush (145)	10 (6.8%)	4 (2.7%)	0 (0%)	64 (44.1%)	49 (33.7%)	25 (17%)	3 (2.0%)	4 (2.7%)	14 (13.5%)
TBLB + EBBX (95)	1 (7%)	6 (6.3%)	0 (0%)	41 (43.1%)	34 (35.7%)	14 (14.73%)	3 (3.1%)	2 (2.1%)	7 (6.7%)
TBLB + EBUS (55)	4 (7.2%)	7 (12.7%)	1 (1.8%)	20 (36.3%)	19 (34.5%)	13 (23.6)	2 (3.6%)	1 (1.8%)	12 (11.6%)
TBLB + Brush + EBUS (52)	0 (0%)	0 (0%)	1(1.9%)	23 (44.2%)	18 (34.6%)	9 (17.3%)	1(1.9%)	1 (1.9%)	1 (0.9%)
TBLB + EBBX + Brush (48)	5 (10.4%)	2 (4.1%)	0 (0%)	16 (33.3%)	14 (29.1%)	12 (25%)	4 (8.3%)	2 (4.1%)	7 (6.7%)
TBLB + EBBX + EBUS (66)	5 (7.5%)	3 (4.5%)	1 (1.5%)	22 (33.3%)	25 (37.8%)	16 (24.2%)	2 (3.0%)	1 (1.5%)	9 (8.2%)
TBLB + EBBX + Brush + EBUS (49)	6 (12.2%)	1 (2%)	0 (0%)	20 (40.8%)	14 (28.5%)	13 (26.5%)	2 (4.0%)	0 (0%)	7 (6.7%)
EBUS (48)	2 (4.16%)	2 (4.16%)	0 (0%)	19 (39.5%)	17 (35.4%)	9 (18.7%)	2 (4.1%)	1 (2.0%)	4 (3.8%)
EBUS + Brush (14)	0 (0%)	0 (0%)	0 (0%)	5 (35.7%)	5 (35.7%)	3 (21.4%)	0 (0%)	1 (7.1%)	0 (0%)
EBBX (18)	2 (11.1%)	2 (11.1%)	1 (5.5%)	10 (55.5%)	5 (27.7%)	2 (11.1%)	1 (5.5%)	0 (0%)	5 (4.8%)
EBBX + EBUS (3)	0 (0%)	0 (0%)	0 (0%)	2 (66.6%)	0	1(33.3%)	0(0%)	0(0%)	0 (0%)
EBUS + EBBX + Brush (3)	0 (0%)	0 (0%)	0 (0%)	2 (66.6%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)

*Classification

No bleeding:

No intervention needed; no blood suctioned continuously. Bleeding stops spontaneously.

Mild bleeding:

Continued suctioning of blood from the airways.

Bleeding stops spontaneously.

Moderate bleeding:

Intubation of the biopsied segment with the bronchoscope

into the wedge position.

Use of adrenaline or cold saline to stop bleeding.

Severe bleeding:

Placement of bronchus blocker or catheter, applying fibrin sealant

Resuscitation, blood transfusion, admission to critical care unit or death

We compared the risk of bleeding for patients with a serum creatinine of 2 mg/dL or higher with 3 mg/dL or higher and we found no statistical difference. Table 4

Table 4: Bleeding complications based on Creatinine levels

	Bleeding complications	No Bleeding complications	*P value*
≤ 2 mg/dL (N=834)	96	738	0.83
>2 mg/dL(N=59)	7	52	
≤ 3 mg/dL(N=867)	99	768	0.54
> 3mg/dL (N=27)	4	23	

Logistic regression revealed that bleeding was more likely if procedure was done under general anesthesia (p = 0.046). In patients with Moderate/Severe bleeding only (excluded mild bleeding) Logistic regression did not reveal any predictors of bleeding.

Discussion:

Our study does not reveal any association between bleeding after common bronchoscopic procedures and stages of CKD or a specific creatinine number. There was no difference in number of biopsies performed in CKD 4 and 5 compared to CKD 1-3. The number of biopsies/EBUS passes was not associated with bleeding risk in this cohort.

Increased bleeding risk with bronchoscopy in patients with renal failure has been reported in the literature. An analysis of 82,059 procedures by Tukey et al. revealed that complications associated with transbronchial biopsy were uncommon with 0.58% of cases associated with procedure related hemorrhage. Presence of renal failure, cirrhosis, older age and female sex were associated with higher risk of procedure related hemorrhage (11).

Pathophysiology of uremic bleeding in patients with CKD is incompletely understood but probably involves dysfunctional von Willebrand factor, increased levels of cyclic AMP and cyclic GMP, uremic toxins and anemia (12). There are no clear guidelines regarding chronic kidney disease and contraindications to bronchoscopy. The guidelines are vague and suggest uremia or serum creatinine higher than 3 mg/dLto be a relative contraindication for bronchoscopy (13, 14). The British Society guidelines in 2013 stated a higher bleeding complication of bronchoscopic biopsy and TBNA in patients with renal failure with or without hemodialysis (7). Real world practice varies; a survey of pulmonologists revealed that 55% of them did not consider an elevated creatinine as absolute contraindication for bronchoscopy. In the same survey 21.6 % felt it was unsafe to perform biopsies in patients with serum creatinine of > 3 mg/dL(15).

Mehta et al reported 1170 bronchoscopies of which 72 patients had a BUN of 30 mg/dL and/or a serum creatinine of more than 2 mg/dL. Of the 25 biopsies performed in this study the complication rate was 8% (16). Bleeding rate in our study was 11% and majority was mild bleeding. The higher rate could be related to a stricter definition of bleeding, inclusion of patients with immunosuppression, chronic liver diseases, and elderly among others factors considered to be high risk for bleeding. Contrary to other studies, we found no increase in bleeding based on absolute creatinine levels with either a creatinine cut off of 2 mg/dL or 3mg/dL. Contrary to the assumption that higher number of biopsies performed in patients with CKD could lead to more bleeding, our study proved this not to be correct.

In general, performance of TBLB is associated with increased risk of bleeding; clinically significant bleeding has been reported in 1-2% of patients undergoing biopsy, including TBLB (7, 17). Our study showed an overall rate for bleeding for patients with CKD undergoing TBLB of 13.2%, and of 8.3% for patients undergoing only EBUS-TBNA, mainly minor or moderate bleeding. We believe this data represent actual practice data as we included patients with immunosuppression or chronic liver disease which may have been excluded in other reports (18).

In order to minimize uremic complications in patients with ESRD, performance of dialysis on the day prior to surgery is recommended (19,20). In Mehta study, ESRD patients were dialyzed 24 hours prior to the procedure (16). Desmopressin is generally administered prior to procedures to decrease bleeding. One study reported no significant reduction in bleeding with its use, however patients with GFR <15 ml/min could benefit (21). Our study found no association between the use of desmopressin and bleeding, but it was given in 6 ESRD patients prior to the procedure which potentially could have decreased the risk.

It has been suggested that pulmonary hypertension is associated with an increased risk of hemorrhage and should be considered a contraindication for TBLB(4). Subsequent studies showed that in patients with echocardiographic evidence of pulmonary hypertension, transbronchial and endobronchial biopsies and EBUS-TBNA were safe

procedures (22,23). As expected, the incidence of pulmonary HTN was higher in patients with CKD 3 to 5. Our study validates the lack of correlation of pulmonary HTN and bleeding in patients with CKD.

Bronchoscopy under general anesthesia was associated with an increase in bleeding rate in our study. In our institution all EBUS and high risk cases are done under GA. In patients with Moderate/Severe bleeding only (excluded mild bleeding) Logistic regression did not reveal any predictors of bleeding. However our findings of higher bleeding rates of bleeding under general anesthesia needs to be studied further.

There are many strengths of our study. First, we included a large cohort of patients undergoing the most common bronchoscopic procedures performed in routine practice by pulmonologist, including EBUS-TBNA. Second, this is the first study correlating different CKD stages and bleeding risk. Third, the study was done in a teaching institution, where procedures are performed with fellows at different stages of training which potentially could increase risk for complications. This reflects a real-world practice in training programs. Conversely, because the study was conducted as part of training program, there is a more structured approach to the pre bronchoscopy evaluation, and the procedural techniques which could identify potential bleeding risk ahead of time. The fellows are required to present all bronchoscopic procedures scheduled in the morning report and this is a failsafe mechanism to follow the protocol. Lastly we used a strict definition for classification of bleeding and included patients with mild bleeding to prevent bias. In patients receiving aspirin or other antiplatelets or anticoagulants, we followed the divisional policy to stop these prior to bronchoscopy. Finally, we attempted to separate each bronchoscopic procedure to estimate bleeding risk with each bronchoscopic procedure.

There are few limitations of the study. This was a retrospective study conducted in a single center teaching institution. Our institution provides services to one of the poorest inner-city community with multiple comorbid conditions which potentially could increase bleeding rate, so its findings could not be generalized.

Conclusion:

In summary, our study shows that in a general pulmonary teaching practice, the overall risk of bleeding associated with bronchoscopy in patients with CKD is low. We demonstrated that CKD does increase bleeding complications especially for patients undergoing TBLB. Most of bleeding complications were mild or moderate and did not required major interventions. Risk of severe bleeding post bronchoscopic biopsy is low. We found no correlation between stage of CKD disease or use of empirical serum creatinine cut off and risk of bleeding. There was no correlation between the number of biopsies performed and risk of bleeding. We suggest that if a bronchoscopic procedure is considered beneficial, the presence of CKD should not deter the bronchoscopist to perform the procedure. However, a careful pre procedure evaluation and planning cannot be overemphasized to minimize risk of bleeding in that potentially frail group of patients.

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