Original Article

DOI: 10.7860/JCDR/2025/74532.20770

Pathology Section

Heterogeneity in the Histopathological Features of Cystic Lesions of the Kidney with Special Reference to CK7 IHC in Cystic Renal Tumours: A Cross-sectional Study from a Tertiary Care Centre

PAKAM DINUSHA[1], THEJASWINI VALLAPUREDDY[2], DIVYA TEJESWI GOPIDESI[3], VIJAYALAKSHMI MURAM REDDY[4], K DURGA[5]

ABSTRACT

Introduction: Renal cystic lesions are the most commonly encountered kidney pathologies, which can fall into developmental, acquired, genetic, infectious and neoplastic categories. Prompt histological diagnosis, in co-ordination with radiological findings, is very important for the further management of these lesions.

Aim: To study the histopathological features of renal cystic lesions and to examine the immunological expression of Cytokeratin 7 (CK7) in cystic renal tumours.

Materials and Methods: The present study is a cross-sectional study conducted in the Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India. Study was conducted over a period of five years, from June 2018 to May 2023, both prospectively and retrospectively. It includes 38 cases of cystic renal lesions out of 147 kidney specimens, which included cyst walls and nephrectomy specimens. Out of the 38 cystic renal lesions, 11 cases of cystic renal tumours were identified. Cytokeratin 7 Immunohistochemistry (IHC) was performed on these 11 cases of cystic renal tumours. Only diffuse membranous or cytoplasmic immunostaining in tumour cells is considered positive, while weak or focal immunostaining is considered negative. The data was entered into Microsoft (MS) Excel sheet and descriptive measures obtained included frequencies and percentages.

Results: Among the 38 cases of cystic renal lesions, the most common were 17 cases of simple cysts, followed by 10 cases of clear cell renal cell carcinoma with a cystic component, three cases of acquired cystic disease, three cases of renal dysplasia, two cases of hydatid cyst, one case of mucinous cyst, one case of adult polycystic kidney disease and one case of a cystic renal neoplasm of low malignant potential. All 11 cases of cystic renal tumours exhibited clear cell morphology. Cytokeratin 7 immunostaining was performed on the 11 cases of cystic renal tumours, of which only the lining cells in a single case of cystic renal neoplasm of low malignant potential showed both intense and diffuse cytoplasmic positivity. The remaining 10 cases of clear cell Renal Cell Carcinoma (RCC) were negative, showing no immunoreactivity.

Conclusion: Renal cystic lesions encompass a broad range of pathologies that have many overlapping features on histopathology. The use of immunohistochemical markers aids in differentiating low malignant potential cystic renal tumours from malignant ones.

Keywords: Cystic renal lesions, Cystic renal tumours, Cytokeratin 7, Immunohistochemistry

INTRODUCTION

Renal cystic lesions are among the most common and fascinating pathologies of the kidney. They are so prevalent that they are found in approximately 40% of patients who undergo imaging studies [1]. Renal cystic lesions can be focal, multiple, unilateral, bilateral, congenital, or acquired, representing a diverse spectrum. The paediatric onset cystic diseases include autosomal recessive polycystic kidney disease, nephronophthisis and multicystic renal dysplasia. The adult-onset cystic diseases consist of simple cysts, acquired cystic kidney disease, Autosomal Dominant Polycystic Kidney Disease (ADPKD), medullary cystic diseases and cystic renal tumours. The management of these cystic lesions depends on their radiological findings and the functional capacity of the affected kidney. To standardise the characterisation of the cysts radiologically, the Bosniak classification was introduced. The Bosniak classification includes four different classes for cystic lesions [2]. The lesions subjected to histological review will be either Bosniak III, IV, or IIF, which have attained complexity in the follow-up scans.

In the present study, the histological spectrum of cystic lesions of the kidney was examined and they were categorised into the following groups: developmental, genetic, infectious, acquired and malignant categories. The diversity of the histopathological features of cystic lesions of the kidney and the expression of cytokeratin 7 IHC in cystic renal tumours were also studied.

The aim of the present study was to study the histopathological features of renal cystic lesions and to examine the immunological expression of CK7 in cystic renal tumours. The objectives were to study renal tumours with cystic components and categorise them according to the latest World Health Organisation (WHO) classification [3]; to investigate cystic lesions associated with renal tumours; to classify the cystic lesions of the kidney into developmental, genetic, infectious, acquired and malignant categories.

MATERIALS AND METHODS

The present study is a cross-sectional study conducted in the Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India, conducted both prospectively and retrospectively over a period of 5 years from June 2018 to May 2023 (IEC no: 43).

Inclusion criteria: All kidney specimens with evidence of cystic components in microscopy are included in the study.

Exclusion criteria: Kidney specimens without any evidence of cystic components, either grossly or microscopically, are excluded from the study.

Sample size: A total of 147 kidney specimens were studied, which included nephrectomies and cyst wall biopsies. Of these, 43 renal tumours and 38 cystic lesions of the kidney were included in the study.

Study Procedure

Microscopic slides of the included cases were reviewed. Clinical histories, including patient details, presenting complaints and any history of past urological interventions, were collected from the medical records. Ultrasound findings and Computed Tomography (CT) findings, along with Bosniak classification [2], were also gathered from the medical records.

The kidney specimens and their microscopic slides that fall under the category of cystic renal tumours were segregated. Gross and microscopic evidence of cystic areas was studied. Necrotic areas and haemorrhagic areas were identified through microscopic examination and only true cystic areas were selected. Paraffin blocks of the representative histologic sections containing true cystic areas were separated. Immunohistochemistry with CK7 was performed using standard protocols. Three-micron sections were taken. After deparaffinisation, antigen retrieval was done using microwave incubation. After Tris buffer wash, slides were treated with 3% H_2O_2 for 5-10 minutes to remove endogenous peroxidase activity. Slides were covered with the primary antibody (Pathnsitu) for 30 minutes. After Tris buffer wash, the slides were treated with HRP-labeled secondary antibody for 30 minutes. Di-amino benzidine and chromogen were added and the mixture was allowed to sit for 5-10 minutes. Counterstaining with haematoxylin was performed and the slides were mounted. Throughout the entire procedure, precautions were taken to ensure that the IHC slides did not dry out. The tubules in the adjacent normal kidney histology were taken as the positive control. Only diffuse and intense membranous or cytoplasmic staining of the clear cells in the tumour area was considered positive, while weak or focal staining was considered negative.

STATISTICAL ANALYSIS

The collected data from the medical records were entered into an MS Excel sheet. Numerical data was entered as is and categorical data was appropriately coded. The descriptive measures obtained included frequencies and percentages.

RESULTS

A total of 43 renal tumours were noted, of which 35 cases were malignant renal tumours and eight were benign tumours. Additionally, a total of 38 cystic lesions of the kidney were identified. Out of the 38 cases of cystic lesions, 26 were males and 14 were females. The majority of the cystic lesions in the kidneys occurred in the age group of 50 years and older. Three paediatric cases were included in the study. Out of the 38 cases, three lesions were paediatric cystic lesions, while 35 cases were adult cystic lesions [Table/Fig-1]. Among the 38 cases, 15 were seen in the age group of less than 50 years and 23 were seen in the age group of greater than 50 years. Out of the 38 cystic lesions, three lesions were developmental, one was genetically related, two were infectious cystic lesions, 21 were acquired cystic lesions and 11 were malignant cystic lesions [Table/Fig-2].

Category of cystic lesions	Number (n)	Percentage (%)
Paediatric cystic lesions	03	7.8
Adult cystic lesions	35	92.2
Total	38	100

[Table/Fig-1]: Number of cystic lesions in the paediatric and adult age groups.

Categories of lesions	Number (n)	Percentage (%)
Developmental	03	7.8
Genetic	01	2.6
Infectious	02	5.2
Acquired	21	55.2
Malignant	11	28.9
Total	38	100

[Table/Fig-2]: Different categories of renal cystic lesions in the present study.

The most common cystic kidney lesions were simple cysts, accounting for 44.7%, followed by 10 cases of clear cell renal cell carcinoma with a cystic component, three cases of acquired cystic disease, three cases of renal dysplasia, two cases of hydatid cyst, one case of mucinous cyst, one case of adult polycystic kidney disease and one case of cystic renal neoplasm of low malignant potential [Table/Fig-3].

Diagnosis	Number (n)	Percentage (%)
Simple cysts	17	44.7
Acquired cystic kidney disease	03	7.8
Mucinous cyst	01	2.6
Adult polycystic kidney disease	01	2.6
Cystic renal neoplasm of low malignant potential	01	2.6
Hydatid cyst	02	5.2
Renal dysplasia	03	7.8
Clear cell renal cell carcinoma with cystic component	10	26.3
Total	38	100

[Table/Fig-3]: Histopathological diagnosis of the renal cystic lesions in the present study.

All paediatric cystic lesions were multicystic renal dysplasia. One case of autosomal dominant polycystic kidney disease was present, which was already a known case; the patient underwent renal transplantation in 2015 for the right kidney. This patient also had multiple cysts in the liver. The gross and histopathological features of renal cystic lesions are mentioned [Table/Fig-4a-j].

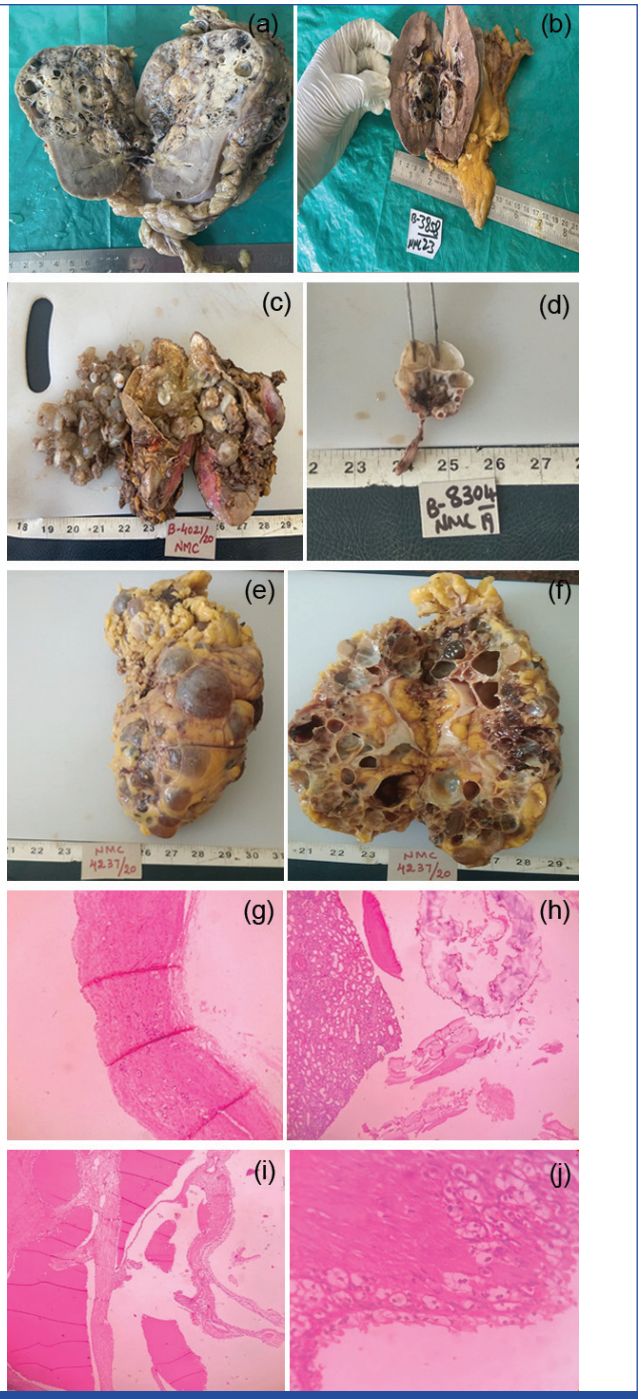
Of the total 43 renal tumours, 11 tumours had cystic components. All of them were malignant and showed clear cell morphology. Ten of them were clear cell renal cell carcinoma and one was a cystic renal neoplasm of low malignant potential. No benign tumour showed a cystic component in the present study.

Out of the 43 renal tumours, five cases showed associated cystic lesions. Four of these were malignant and one case was benign, diagnosed as oncocytoma. All five cases were associated with simple renal cysts.

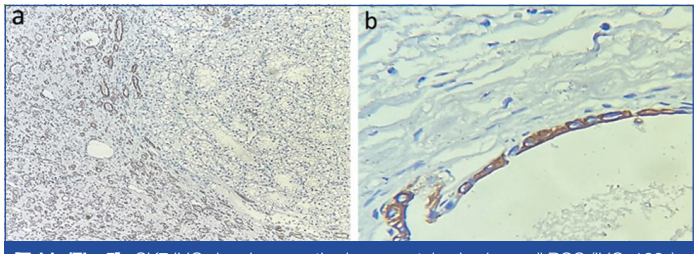
Cytokeratin 7 immunohistochemistry was performed on all 11 cases of cystic renal tumours, of which only the single case of cystic renal neoplasm of low malignant potential showed both diffuse and intense positivity in the lining cells. In the 10 cases of clear cell renal cell carcinoma with cystic components, the clear cells showed no immunoreactivity with CK7. The tubules in the adjacent normal kidney showed positivity [Table/Fig-5a,b].

DISCUSSION

Cystic lesions of the kidney belong to a wide range of categories with heterogeneous histopathological features, unlike cystic lesions of other organs, which are usually developmental or neoplastic entities. Cystic lesions of the kidney can present as associated components of renal tumours or as cystic components within the tumour. Renal cystic diseases and cystic renal tumours have many overlapping features, posing diagnostic challenges. Based on the aetiology, these cystic lesions can be categorised into developmental, genetic, acquired, malignant and cysts associated with systemic disease [4]. The developmental cystic lesions include multicystic renal dysplasia.



[Table/Fig-4]: a) Gross image of renal cell carcinoma showing variegated appearance with cystic areas; b) Gross image of cystic renal neoplasm of low malignant potential showing multiloculated cystic lesion with septations; c) Gross image of hydatid disease in kidney showing hydatid sand with multiple daughter cysts; d) Gross image of multicystic renal dysplasia showing atrophic kidney and cystic areas; e) Gross image of Autosomal Dominant Polycystic Kidney Disease (ADPKD) showing enlarged kidney and multiple cysts over external aspect; f) Gross image of ADPCKD on cut section showing multiple cystic of varying sizes and loss of corticomedullary differentiation; g) Microscopy of a simple renal cyst showing flattened to low cuboidal lining epithelium (H&E, 100x); h) Microscopy of hydatid disease of kidney shows normal renal parenchyma with adjacent laminated membrane of the organism (H&E, 400x); i) Microscopy of cystic renal neoplasm of low malignant potential showing multiloculated cysts (H&E, 100x); j) Microscopy of cystic renal neoplasm of low malignant potential showing cyst wall lined by cells with clear cytoplasm (H&E, 400x).



[Table/Fig-5]: CK7 IHC showing negative immunostaing in clear cell RCC (IHC, 100x); b) CK7 IHC showing positive immunostaining in lining cells of cystic renal neoplasm of low malignant potential (IHC, 400x).

Genetic cystic lesions include autosomal recessive polycystic kidney disease, ADPKD, juvenile nephronophthisis, medullary cystic kidney disease and glomerulocystic kidney disease. Acquired cystic lesions include simple renal cysts, acquired cystic renal disease and medullary sponge kidney. Malignant cystic lesions include renal cell carcinoma with cystic degeneration and Multilocular Cystic Renal Neoplasm of Low Malignant Potential (MCRNLMP). Identification of potential preneoplastic lesions, such as papillary adenoma, clear cell cysts, cysts lined by eosinophilic atypical epithelium and intracystic papillary epithelial proliferation, is important to assess further risk [5].

Multicystic renal dysplasia is characterised by anomalous differentiation of the metanephros, leading to disorganised development of the kidney. It is the most common cause of abdominal mass in newborns and the most common cystic disease of the kidney in children. Most of these cases are diagnosed during foetal ultrasound imaging [6] and in 24% of cases, spontaneous regression is achieved [7]. Unlike other hereditary cystic kidney diseases, the renal parenchyma in multicystic dysplasia is non functional [8]. The kidney appears as a large reniform mass with multiple cysts. Microscopically, the cysts are lined by cuboidal epithelial cells and are surrounded by immature mesenchymal elements.

The hydatid cyst is one of the important zoonotic diseases caused by the cestode *Echinococcus granulosus*. The infection is caused by orofaecal contamination due to the transmission of parasite eggs by infected vegetables. The liver and lungs are the most commonly involved sites, while it is rarely seen in the heart, brain, soft tissues, kidney and head and neck. The existence of a hydatid cyst in the human body, with or without symptoms, is defined as hydatid disease. Renal hydatid cysts may be silent for years and may result in irreversible organ damage. Imaging to estimate the size of the cysts and the use of scolicidal drugs before the operation are very important. Microscopically, the cyst wall shows the laminated membrane along with scolexes and brood capsules of the organism.

A simple renal cyst is an area of fluid collection within the kidney. Its size ranges from a few millimeters to more than 10 cm. The cyst usually contains straw-coloured fluid. Microscopically, the cyst wall is lined by flattened to low cuboidal epithelium. Simple renal cysts are the most common cystic lesions of the kidney, seen in 5% of the general population and account for 65-70% of renal masses [9]. There is an association between hypertension and simple cysts. Most of the time, they are asymptomatic, but sometimes they can impair the functioning of the kidney. The risk of malignancy in a simple cyst is 1.7% [10]. Ritchie R et al., reported an incidental finding of malignancy within a marsupialised simple renal cyst [11]. In cases of doubt, a rapid intraoperative frozen section study of the cyst wall may be useful to prevent dissemination after deroofing the cyst wall.

Mucinous cystic neoplasms of the kidney are extremely rare, with less than 50 cases reported to date. A 45% of these cases have been associated with renal lithiasis [12]. Long-standing chronic inflammation and renal calculi may be possible aetiological factors [13]. Grossly, these neoplasms can be unilocular or multilocular. Microscopically, they are characterised by tall mucin-secreting columnar epithelium. In the present study, the patient has no history of urolithiasis. A similar case with no history of urolithiasis was reported by Xiang H et al., [14].

A multilocular cystic renal neoplasm of low malignant potential is a tumour composed entirely of numerous cysts, the septa of which contain individual or groups of clear cells without expansile growth. It accounts for less than 1% of all renal tumours. The updated WHO classification of renal tumours classifies multilocular cystic RCC as a cystic renal neoplasm of low malignant potential [3]. No tumours with these features have ever been reported to recur or metastasise. The tumour consists exclusively of variable-sized cysts separated by thin fibrous septa and filled with clear, serous, or gelatinous fluid.

The microscopic diagnostic feature is the presence of tumour cells within the fibrous septa without expansile growth. The tumour cells should be similar to those lining the cysts [3].

Acquired cystic disease has been defined as the presence of five or more cysts in each kidney, as observed radiologically [15,16]. Feiner HD et al., suggested that acquired renal cystic disease should be defined as the cystic change of at least 40% of the kidney volume [17]. It develops in both haemodialysis patients and CAPD patients [18]. Konda R et al., have shown that both hepatocyte growth factor and c-Met are overexpressed in the cystic epithelium [19]. The activation of the proto-oncogene c-jun may play a role in the aberrant proliferation of hyperplastic atypical cells in ARCD and the subsequent development of RCC. The size of the kidney is grossly reduced, with multiple cysts giving it a spongy appearance. Microscopically, the cysts are lined by flattened to cuboidal epithelium.

Acquired cystic renal disease can result in renal tumours such as oncocytoma, chromophobe carcinoma, acquired cystic disease-associated renal cell carcinoma and clear cell papillary renal cell carcinoma in end-stage disease [20,21].

Autosomal dominant polycystic kidney disease is one of the most common hereditary conditions, characterised by expanding cysts that progressively destroy the renal parenchyma. Its incidence is 1 or 2 in 1,000 live births. It is caused by mutations in the PKD1 and PKD2 genes [22]. It is usually bilateral, although significant asynchrony may be noted. The surface of the kidney appears bosselated with variable-sized cysts. Microscopy shows a loss of corticomedullary differentiation. The entire renal parenchyma demonstrates multiple cysts lined by flattened to low cuboidal epithelium.

Cystic degeneration in clear cell renal cell carcinoma is very common, along with other degenerative changes such as necrosis and haemorrhages. Clear cell renal cell carcinoma is the most common malignant tumour of the kidney, which is morphologically heterogeneous and composed of clear or eosinophilic cells. It accounts for 65-70% of all renal cancers. Vessel formation and a typical molecular background are characteristics of this tumour. Grossly, these tumours are golden yellow due to their high lipid content. Microscopic features are diverse, displaying solid, alveolar and acinar patterns. Sarcomatoid and rhabdoid differentiation occurs in 5% of tumours, which has a worse prognosis [14].

True cystic renal tumours include mixed epithelial and stromal tumours, MCRNLMP, eosinophilic solid and cystic renal cell carcinoma, tubulocystic RCC and fumarate hydratase-deficient RCC with a tubulocystic pattern [23]. Others are conventional renal tumours with cystic variants.

Searching for solid areas, identifying focal tubulocystic architectural patterns and examining cell morphology are important in the diagnosis of cystic renal tumours. Immunohistochemistry for CK7 and CA IX is helpful in differentiating cystic renal tumours exhibiting clear cell morphology.

Cytokeratin 7 positivity is observed in MCRNLMP, clear cell renal cell tumours [24] and tubulocystic RCC, among the tumours with clear cell morphology. Immunohistochemistry of CK7, CK20 and CD117 is helpful in differentiating cystic renal tumours with eosinophilic cell morphology.

Cytokeratin 7 is an intermediate filament that can be expressed in many normal epithelia and epithelial tumours. CK7 is the first trial universal marker used in renal epithelial tumours. The positivity of CK7 can be variable in clear cell renal cell carcinoma, depending on the histological grade and architectural growth patterns [25]. CK7 positivity in clear cell RCC with a cystic component can be seen in macrocystic spaces and pseudopapillary areas [26]. When there is diffuse and intense staining with CK7 in clear cell RCC, the diagnosis is mostly unlikely and we need to exclude further possibilities [27].

Limitation(s)

Only 11 cases of cystic tumours were studied, of which only one case of MCRNLP was identified. All 11 cases exhibited clear cell morphology. Only one IHC marker, CK7, was used; however, a panel of IHC markers would have been more useful.

CONCLUSION(S)

Cystic kidney diseases are diverse and common lesions that pose a diagnostic challenge due to overlapping features. Histopathological characterisation of cystic lesions, along with radiological findings, helps to predict the genetic or acquired nature of the disease and also to assess the future risk of developing tumours. Cystic renal tumours include true cystic renal neoplasms and cystic variants of conventional renal tumours.

IHC markers CK7, CK20 and CD117 are helpful in differentiating cystic renal tumours when the tumours exhibit overlapping morphological features, such as MCRNLP and Cystic Clear Cell Renal Cell Carcinoma (CC-RCC). When there is intense and diffuse staining with CK7 IHC present in a clear cell renal cell carcinoma, we need to exclude other entities such as MCRNLP and clear cell renal cell tumours.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Government Medical College, Ongole, Andhra Pradesh, India.
2. Assistant Professor, Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India.
3. Assistant Professor, Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India.
4. Professor, Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India.
5. Professor and Head, Department of Pathology, Narayana Medical College, Nellore, Andhra Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. K Durga,
3rd Floor, Department of Pathology, Narayana Medical College Building,
Nellore-524003, Andhra Pradesh, India.
E-mail: drkdurga60@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 24, 2024
- Manual Googling: Nov 04, 2024
- iThenticate Software: Nov 30, 2024 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Aug 23, 2024**
Date of Peer Review: **Sep 24, 2024**
Date of Acceptance: **Dec 02, 2024**
Date of Publishing: **Mar 01, 2025**