Introduction: The etiopathogenesis of pelviureteric junction obstruction (PUJO) has been debated. Recently, the role of interstitial cells of Cajal-like cells (ICC-LC) has been studied and reported to be the cause of this functional obstruction. We studied the histopathology and ICC-LC density at PUJ and compared it with that of PUJ of the control group and distal ureteric margin of the study group.

Methods: A prospective study was conducted which included PUJO patients in the study group and the renal tumor patients in the control group. Histopathological examination (muscle hypertrophy and fibrosis) and immunohistochemistry (ICC-LC density) were done. The muscle hypertrophy, fibrosis, and ICC-LC density at the PUJ in both the groups were compared. A similar comparison was performed between the findings at the PUJ and the distal margin in the study group.

Results: The study and control groups included 37 PUJO patients and 13 Wilms tumor patients. The ICC-LC density at PUJ in the study group was significantly lower than that in the control group \( (P < 0.001) \) and that at the distal resected margin of the study group \( (P < 0.001) \). Significantly increased muscle hypertrophy \( (P < 0.001) \) and fibrosis \( (P = 0.002) \) were seen at PUJ in the study group compared to the control group. No significant association was noted between the ICC-LC density and muscle hypertrophy at PUJ and the distal resected margin in the study group.

Conclusion: A significant decrease in the density of ICC-LC and increased fibrosis and muscle hypertrophy at PUJ in children with PUJO play a role in the etiopathogenesis of the disease.

Keywords: Hydronephrosis, interstitial cells of Cajal-like cells, interstitial cells of Cajal, pelviureteric junction obstruction
as pacemaker cells in the gastrointestinal tract in humans. \cite{15} Cells similar to ICC in the gastrointestinal system were discovered in the urinary tract. \cite{16} To differentiate them from the ICC of the gastrointestinal tract, they were named ICC-LC. Few authors have investigated the role of ICC-LC in the motility of the urinary tract. \cite{2,17,18} These ICC-LC act as pacemaker cells and can generate spontaneous slow waves to initiate smooth muscle peristalsis and work as a link between nerves and smooth muscles. The role of ICC-LC has been emphasized in modulating the transmission of peristaltic waves across PUJ and in the etiopathogenesis of PUJO. \cite{16}

Studies regarding the expression of C-kit-positive ICC-LC in the upper urinary tract have been published, but no common consensus has been reached. \cite{1,4-10} Furthermore, these studies have reported conflicting results with an increase, decrease, and no change in ICC-LC density at PUJ.

This study was planned to investigate the ICC-LC expression and histopathology in the PUJ specimens at the PUJ and distal resected margin of the ureter. The variation in the density of ICC-LC and histopathology may have a role in the development of hydronephrosis, with decreased motility at the PUJ leading to decreased urine flow across it.

**METHODS**

**Study population**

Ethical clearance was obtained from the institute ethics committee (IECPG-88/22.3.2017, RT-08/2017). A cross-sectional comparative study was conducted in the Department of Pediatric Surgery from August 2017 to April 2019.

- **Study group inclusion criteria:**
  - PUJO patients who underwent Anderson–Hynes pyeloplasty
  - Informed written consent for participation in study.
- **Study group exclusion criteria:**
  - Patients who underwent redo-pyeloplasty for previous failed surgery
  - Insufficient or damaged operative specimen.
- **Control group inclusion criteria:**
  - Children with renal tumors who underwent nephroureterectomy with no involvement of PUJ or ureteral extension.

All the patients in the study group underwent Anderson–Hynes pyeloplasty by an open approach. Intraoperative findings were noted. Part of the dilated pelvis along with the PUJ was excised. The specimen was resected until the normal caliber of the ureter was reached. The specimen was excised in continuity and the apparent PUJ was labeled before submitting for histopathology and immunohistochemistry. The transverse sections from the PUJ and the distal end of the specimen were used for further analysis. The postoperative outcome of the study group was evaluated with clinical history, examination, ultrasonography, and renal dynamic scan at 3 months. We studied the histopathology and ICC-LC density at PUJ and compared it with that of PUJ of the control group. We also compared these findings at the PUJ and distal ureteric margin of the study group.

**Histological examination**

Histopathology was examined using hematoxylin and eosin stain. Sections were examined using an Olympus BX 43 microscope for the presence of fibrosis and muscle hypertrophy and disarray. Muscle layer thickness and appearance were compared with those of age-matched control tissue. Muscle hypertrophy was defined by increased thickness of the muscle layer, with or without the disarray of the muscle fibers and or intermyocyte fibrosis. The total thickness of the muscle layer at the site of PUJO and control ureter tissue specimens was objectively measured by computer-assisted image analysis software Image-Pro Plus 6.1, Media Cybernetics, USA, and compared between the groups. Measurements were made on digital images taken at ×40 magnification and muscle thickness was measured in multiples at the oriented areas longitudinally, as shown in Figure 1, and expressed in the micrometer scale. In the absence of an established quantitative histological grading scale, the measured values were not further subgraded.

Muscle hypertrophy was graded as follows: Grade 0: when the thickness of the muscle layer was equal to the thickness of age-matched controls and Grade 1: increased thickness of the muscle layer compared to age-matched controls, with or without a disarranged arrangement of muscle fibers and intermyocyte fibrosis.

Fibrosis was defined by increased laying down of extracellular matrix identified by the deposition of collagen and fibronectin, and was subgraded as

**Figure 1:** Photomicrographs showing muscle hypertrophy (arrows) (a ×40) and fibrosis (b ×40) at the site of pelviureteric junction.
Immunohistochemistry

Tissue sections of 4–5 microns were cut on the coated slides. Slides were then dewaxed. Peroxide blocking was applied for 30 min, followed by dipping in double-distilled water. Antigen retrieval was performed using the citrate buffer (pH = 6) at 100°C for 30 min. Tissue sections were then allowed to cool down to room temperature and dipped in double-distilled water. Sections were dipped in three changes of tris buffer (pH 7.5) for 5 min each. The primary antibody (c-kit antibody) was applied and incubated overnight at 4°C. A universal secondary antibody was applied. The reaction color was developed by 3,3-diaminobenzidine. Slides underwent dehydration in graded alcohol, cleaned in xylene, mounted with DPX, and viewed under a light microscope using an Olympus BX43 microscope. Ten large magnification areas (×400 magnification/high-power field [hpf]) were counted. The average number of ICC-LC was quantitatively assessed and scored as follows: score 0: 0–1 ICC-LC/hpf, score 1+: 2–5 ICC-LC/hpf, score 2+: 6–10 ICC-LC/hpf, and score 3+: >10 ICC-LC/hpf. The grading system was the same as used by Inugala et al.\(^9\) The location of ICC-LC was evaluated in the lamina propria within and at the interface of the inner circular and outer longitudinal layers. The CD117-stained ICC-LC appeared as spindle-shaped cells compared with smaller round granular positivity of mast cells, which were used as internal controls.

Outcome parameters

The primary outcome assessed was the comparison of the density of ICC-LC at PUJ in the study group and the control group. The density of ICC-LC at the distal end of the specimen was compared with that of PUJ in the study group. The secondary outcome assessed was the comparison of histopathological findings (muscle hypertrophy and fibrosis) at the PUJ and the distal end of the specimen of the study group and the PUJ of the control group.

The association between the histopathological findings and the ICC-LC density was also assessed.

Statistical details

Statistical analysis was done using Stata (StataCorp LLC, College Station, TX 77845, USA). Data were presented as number (%) or median (minimum–maximum) as appropriate. Demographic variables were compared between the two groups using the Wilcoxon rank-sum test, and sex distribution was compared between the two groups using Fisher’s exact test. ICC-LC density, muscle hypertrophy, and fibrosis were assessed using grading and compared between the two groups using the Chi-square test for trend. The association between ICC-LC density with muscle hypertrophy at PUJ and resected margin in the study group was seen using the Chi-square test. Logistic regression was used to determine the association of muscle hypertrophy and fibrosis with groups (study group and control group). The results were reported as odds ratio and 95% confidence interval (CI). \(P < 0.05\) was considered statistically significant.
significantly higher than the control group (1034.1 µm vs. 667.5 µm [P < 0.001]) [Figure 3].

No significant association was noted between the ICC-LC density and muscle hypertrophy at PUJ and the distal resected margin in the study group with \( P = 0.715 \) and 0.097, respectively. On logistic regression analysis, the odds ratio of having PUJO if muscle hypertrophy is present is 39.4 (CI: 6.2–250.1, \( P < 0.001 \)). The odds ratio of having PUJO if fibrosis is present is 8.1 (CI: 1.9–33.5, \( P < 0.001 \)).

It was noted that in the study group, the younger patients had higher ICC-LC density. However, the association was not significant (\( P = 0.6719 \)).

All the patients in the study group were asymptomatic postoperatively. The median (range) follow-up period was 19.2 (14–21) months. The mean differential function on postoperative renal dynamic scan was 43.4% ± 16.6%. All the patients in the study group had nonobstructive drainage postoperatively, therefore, all had a good outcome.

**Discussion**

The cause and nature of abnormality at the PUJ that leads to obstruction has been a matter of debate. Many histopathological findings have been noted at the PUJ in patients with PUJO. William and Kenawi reported absent or deficient muscle, abnormal muscle orientation,
and replacement of muscle by collagen at PUJ in PUJO.\[21\] Gosling and Dixon and Antonakopoulos et al. showed abnormal innervation patterns, abnormalities of smooth muscle, and disorganization of the collagen network at PUJ.\[22,23\] Murakumo et al. observed sparse and thin muscle fascicles at PUJ.\[24\] However, in our study, we found significant muscle hypertrophy at PUJ in PUJO patients compared to controls \((P = 0.0001)\). Significantly more fibrosis was also noted at PUJ in the study group \((P = 0.002)\). The thickness of the muscle layer at the PUJ has been debated in the literature. Bartoli et al.\[25\] reported a loss of muscle layer, whereas Yurtçu et al.\[26\] did not find any change in the thickness of the muscle layer in children with PUJO. Our findings match those observed by Zhang et al.,\[19\] which showed fibrosis and muscular hypertrophy at PUJ in children with PUJO. Interestingly, nearly one-third of our control group patients showed muscle hypertrophy in contrast to the findings of Zhang et al., in which only one of 12 of the controls had thickness >0.4 mm.\[15\] The difference is difficult to explain but can be attributed to the difference in the choice of control groups. In the index study, we had used patients with renal tumors, whereas Zhang et al. had used autopsy specimens of children without any renal or ureteral pathology.

Recent investigators have concentrated on the role of ICC-LC in the etiopathogenesis of PUJO.\[1,4-14\] These researchers have studied the density of ICC-LC at PUJ in PUJO patients and compared it with control [Table 3]. Many authors have reported a significant decrease in ICC-LC density at PUJ in the study group compared to the control group.\[1,4,5,7,8,11-14\] Koleda et al.\[10\] reported a significant increase in ICC-LC density at PUJ in the study group compared to the control group. Apoznanski et al.\[6\] found no significant change in the density of ICC-LC at PUJ in the study group compared to the control group. In our study, a significant decrease in ICC-LC density at PUJ in the study group compared to the control group \((P = 0.001)\) was noted. Differences in results of these studies may be partly attributable to differences in the control taken and the methodology adopted [Table 3]. Most studies have used the 10–11 hpf to examine ICC-LC density, but the number and terminology used to define various grades are heterogeneous, which makes comparison more challenging.

Inugala et al.\[20\] and Kuvel et al.\[5\] compared ICC-LC at PUJ with resected margin in PUJO patients and found a significant decrease in the density of ICC-LC at PUJ. In our study also, on comparing the ICC-LC density at PUJ and resected margin, significantly low ICC-LC density was seen at PUJ \((P = 0.0002)\). Similarly, a statistically significant change was seen in the histopathological findings (muscle hypertrophy and fibrosis) at the resected margin compared with findings at PUJ. No correlation was noted between the histopathological findings and the ICC-LC density. No similar comparison is available as most studies\[9,1,4,8,10,12,20\] have studied only ICC-LC density and not histopathology.

A correlation between age and the density of the ICC-LC at PUJ has also been proposed. Koleda et al.\[10\] showed a significant decrease in the number of ICC-LC with increasing age \((P = 0.0038)\). Apoznanski et al.\[6\] found no significant correlation between the age of PUJO patients and the distribution of ICC-LC \((P = 0.087)\). In our study, the younger PUJO patients had higher ICC-LC density. However, the association was not significant \((P = 0.6719)\).

Inugala et al.\[20\] found fewer ICC-LC at the resected margin to be associated with poor outcome. They included patients with no improvement or worsening drainage and renal function as a poor outcome. However, in our study, all patients had nonobstructive drainage pattern postoperatively and therefore had a good outcome. None of these patients have been reoperated and are on follow-up.

Lang et al.\[17\] have emphasized that c-kit-positive ICC-LC along with atypical smooth muscle cells and c-kit-negative ICC-LC play an integrative role as pacemaker cells. The understanding of electrophysiological profile of the cells in pacemaking and pyloureteric peristalsis is evolving rapidly. This is a limitation of the index study as cells other than c-kit-positive ICC-LC that can also contribute to the pathophysiology of PUJO were not studied.

The strength of our study is that more patients were included in the study group compared to the previous studies. Furthermore, most early studies have either compared ICC-LC at PUJ in children with PUJO and controls or compared ICC-LC at PUJ and distal margin in children with PUJO. The index study was unique to make both comparisons. The study also evaluated the histopathological findings and studied the correlation between the ICC-LC density and the histopathological findings. The limitation of this study is the lack of ideal control, which would be PUJ of an individual with no pathology. Another limitation of the study is the lack of sample. Although the study enrolled the maximum number of patients reported till date, still the sample size was not calculated and hence which affects the certainty of findings to some extent. The study also attempted to study the correlation between the findings at the distal margin and the outcomes, which may have had translational value to predict the outcome of surgery in these children based upon density of ICC-LC.
at the distal margin of the specimen. The study failed to detect any correlation, and with the criteria used, none of the patients had a poor outcome. This could be due to the lack of sensitive parameter to detect minor changes in outcome and small study sample. Moreover, the surgical outcomes in these patients depend upon

Table 3: Summary of literature on interstitial cells of Cajal-like cell density at pelviureteric junction in pelviureteric junction obstruction

| Author               | Year | SG-PUJ | CG-PUJ | SG-RM | Result                                                                 | Methodology                                                                 |
|----------------------|------|--------|--------|-------|------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Solari[1]            | 2003 | 19     | 7      | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC cells in 10 hpf of 0.152 mm²                      |
|                      |      |        |        |       |                                                                         | Grading: Sparse: 0-1                                                        |
|                      |      |        |        |       |                                                                         | Few: 2-3                                                                  |
|                      |      |        |        |       |                                                                         | Moderate: 4-8                                                              |
|                      |      |        |        |       |                                                                         | Many: >8                                                                  |
| Yang et al.[4]       | 2009 | 24     | 21     | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average optical density using Image-Pro Plus professional image analysis system |
| Kuvel et al.[5]      | 2011 | 32     | 30     | 32    | No change in the density of ICC-LC between PUJO and controls. Decreased ICC-LC density at PUJ compared to distal resected margin | Average density of ICC-LC in 10 hpf                                      |
|                      |      |        |        |       |                                                                         | Grading – not used                                                         |
| Koleda et al.[10]    | 2012 | 20     | 5      | Not done | Increased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC cells in 11 hpf of 0.136 mm²                     |
|                      |      |        |        |       |                                                                         | Grading: Sparse: 0-1                                                        |
|                      |      |        |        |       |                                                                         | Moderate: 2-3                                                              |
|                      |      |        |        |       |                                                                         | Many: 4-8 cells                                                            |
| Apoznanski et al.[6] | 2013 | 20     | 5      | Not done | No change in ICC-LC density at PUJ in SG                                | Gradient of ICC-LC cells in 11 neighboring hpf of 0.136 mm²                |
| Eken et al.[7]       | 2013 | 35     | 7      | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC in 10 hpf                                       |
|                      |      |        |        |       |                                                                         | Grading: Sparse: 0-3                                                       |
|                      |      |        |        |       |                                                                         | Few: 4-8 cells                                                             |
|                      |      |        |        |       |                                                                         | Many: >8 cells                                                             |
| Senol et al.[8]      | 2016 | 19     | 12     | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC in 10 hpf                                       |
|                      |      |        |        |       |                                                                         | Grading: Rare: 0-3                                                         |
|                      |      |        |        |       |                                                                         | Few: 4-6 cells                                                             |
|                      |      |        |        |       |                                                                         | Many: >6 cells                                                             |
| Inugala[20]          | 2017 | 25     | Absent | 25    | Decreased ICC-LC density at PUJ compared to distal resected margin     | Total number of ICC-LC cells in 10 hpf                                    |
|                      |      |        |        |       |                                                                         | Grading: Grade 0: 0-1                                                      |
|                      |      |        |        |       |                                                                         | Grade 1+: 2-5                                                              |
|                      |      |        |        |       |                                                                         | Grade 2+: 6-10                                                             |
|                      |      |        |        |       |                                                                         | Grade 3+: >10                                                              |
| Bayrak et al.[12]    | 2019 | 37     | 8      | Not done | Decreased ICC-LC density at PUJ in SG                                  | Grading: Sparse – 0-1                                                      |
|                      |      |        |        |       |                                                                         | Moderate – 2-3                                                             |
|                      |      |        |        |       |                                                                         | Many – 4-8 cells                                                           |
| Babu et al.[13]      | 2019 | 31     | 20     | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC cells in 10 hpf                                 |
|                      |      |        |        |       |                                                                         | Grading – not used                                                         |
| Babu et al.[11]      | 2020 | 31     | Absent | 31    | Decreased ICC-LC density at PUJ compared to distal resected margin     | Average density of ICC-LC cells in 10 hpf                                 |
|                      |      |        |        |       |                                                                         | Grading – not used                                                         |
| Wishahi et al.[14]   | 2020 | 7      | 5      | Not done | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC cells                                           |
|                      |      |        |        |       |                                                                         | Grading – not used                                                         |
| Index study          | -    | 37     | 13     | 37    | Decreased ICC-LC density at PUJ in SG                                  | Average density of ICC-LC cells                                           |

SG-PUJ: Study group pelviureteric junction, CG-PUJ: Control group pelviureteric junction, SG-RM: Study group resected margin, RM: Resected margin, PUJ: Pelviureteric junction, ICC-LC: Interstitial cells of Cajal-like cells, PUJO: Pelviureteric junction obstruction, hpf: High-power field.
multiple factors such as surgical technique and handling of the ureter.

**CONCLUSION**

The study adds to our current knowledge of the etiopathogenesis of PUJO. A significant decrease in the density of ICC-LC and increased fibrosis and muscle hypertrophy at PUJ in children with PUJO and compared to controls. These changes noticed at PUJ in children with PUJO improved at the distal resection margin of the specimen. The density of ICC-LC may have a role in etiopathogenesis of PUJO although no direct association between density of ICC-LC and histopathological findings could be demonstrated.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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