

We are pleased to inform you that, after preview by the Editorial Office and peer review as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 86561, Retrospective Study) basically meet the publishing requirements of the *World Journal of Clinical Cases*. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision.

Dear editors,

Dear reviewers,

Thank you for your time to review our paper. We acknowledge that our paper might have some issues in conformity with the referees' comments. We have addressed them and revised the manuscript accordingly. Changes are visible as highlighted and/or track changes.

We sincerely thank the three reviewers for their thorough and helpful comments and suggestions. We have addressed all of the raised queries and responded to all reviewers' comments.

We believe that you find these changes satisfactory, and the revisions have substantially improved the quality of the manuscript.

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** First of all, I would like to congratulate the authors for conducting this interesting study. However, some points have to be addressed:

- Thank you for the overall evaluation of our paper as good.
  
- 1- In the methodology section: it will be a good addition if immunohistochemistry protocols were sufficiently described. Although authors mentioned they were adhered to the manufacturer's instructions, variations are always expected. The expression of antibodies was not adequately described from one side, and only expressed as positive or negative, it will be excellent if the authors can put it as a percentage, which will give different findings.
  - Thank you for the comment. We completely agree with you that when considering immunohistochemistry in neoplastic diseases, to some extent, the

determination of positive tumor cells in percentage matters, although a smaller percentage does not change the final result and it will always be positive. However, in this particular case, we are not describing the immunohistochemistry of the urothelial carcinoma itself, here we described only that MGCs in each case, and they were entirely - 100% positive.

2- In results: Table 1: Antibodies were written using capital letters and small letters, please adhere to capital letters.

- Thank you for the comment, the remark is completely justified. The correction was made.

3- Figure 2: please add standard deviations into columns for more professional presentation. Other figures: arrows are not always clear.

- Thank you for the great suggestion. As far as we understand the referee, the suggestion is to put +/-SD in the figures. We agree with this suggestion, however, there is no room to put the SD next to the average value.
- We also did our best to make the arrows more visible.
- 3. Conclusion: Conclusion is longer than usual. please make it shorter and up to the study aims
- Thank you for the comment. The correction was made.

4- Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

- Thank you for the overall evaluation of our paper as good.
- **Specific Comments to Authors:** -Abstract: " more often in high-graded". Do you mean high-grades?
- Yes, thank you for the note. The correction was made.
- -Introduction: "Prof. Popescu and his collaborators from Bucharest in 2005 discovered a brand-new entity of interstitial cells in various organs, and they named them telocytes [3,4]" You cite here two references and ignored Popescu studies which are numerous and related to this telocyte. Kindly refer to some of

these articles.

- Thank you for the note. The correction has been made by citing the author and his collaborators.

- -“ Discovered 16 years ago” Better to write since ..

- Thank you for the note. The correction was made.

5- -“Urothelial carcinoma (UC) of the bladder is a multifactorial disease characterized by an aggressive course, frequent recurrences, and high mortality worldwide. The morphology of bladder carcinoma is well known. Still, its stroma is insufficiently studied. Moreover, some of its components, such as mononuclear giant cells and MGCs, are almost unknown” Kindly refer to at least one source here, such as: Wijesinghe HD, Malalasekera A. Giant Cell Urothelial Carcinoma of Bladder. Case Rep Urol. 2021 Jul 15;2021:8021947. doi: 10.1155/2021/8021947.

- Thank you for the note, we cited the author you mentioned.

10. -In methods you should mention the process of diagnosis, if you re-examined H& E slides or no and if yes, you should mention how did y consider the agreement, I realized that you included “76cases with invasive low-grade (LG) and high-grade (HG) UC, but the low grade invasive tumors incidence is low (mostly <5%) so it is recommended to re-examine slides to assure the grading

- We understand the critical note. However, the total number of investigated cases is 3021, of them the Bulgarian patients with UC are 263 (8.7%) and the French patients with UC are 132 (25.5%). The majority of these patients having LG urothelial carcinoma. More data is published here: Gulinac, M., Dikov, D., Velikova, T., & Belovezhkov, V. (2020). Increased PD-L1 expression in high-grade bladder cancer with squamous cell differentiation in Bulgarian and French patients' samples. Annals of diagnostic pathology, 49, 151640. Advance online publication. <https://doi.org/10.1016/j.anndiagpath.2020.151640>

11. -In table1: kindly revise the typing of markers (eg, cd should be CD)

- Thank you for the comment, the remark is completely justified. The correction was made.

12. -Why you mention only ANOVA test in your methods section, however you used other tests ?

- Thank you for the critical note. We indeed mention ANOVA among all the analysis and we used it to search for significance between more than two groups.
- - In results grammar and typo errors are seen 9eg, in well-differentiated UC (G1) - in 6/37 of cases (16.2%). Also presenting these results in table is advised.
- Thank you for noticing that. It seems that this remained after coping the results.
- We agree that we can present the data in Table, however, we are afraid that this would be a very simple and not informative enough table. However, if the referee insists, we will form new tables.
- - Figure 1 can replaced or included in a table
- Thank you for your comment, we agree at some extent. However, we believe that changing this figure to a table will not significantly change the context of the content. And also, we think that these data would be more comprehensive in the form of figure. For this reason, we would like the referee to agree to keep this figure as it is.
- - In histological and IHC figures, you write "Figure x. IHC examination of UC of the bladder", You should replace by something like Figure 4x. CD31 IHC staining of a case of UC; ... (to avoid confusion and to clear the type of marker under corresponding image).
- Thank you for the proposals. We tried to implement the suggestion whenever applicable.
- -Figure 5& 6: revise the power of magnification
- Thank you for the comment. We have performed a revision of which we have not found an error in the magnification.
- - Figure 7 is not seen as a proper differential diagnosis of MGCs, can you explain?

- Thank you for your comment, the error is completely typographical and it has been corrected. Table 7 refers to the diagnostic algorithm (as indicated in the text) and not differential diagnostic.

13. - In discussion; a good review for giant cells in different organs presented,

- Thank you for the note. We did our best to cover the existing literature.

14. - "The role of p16 extends beyond cell "aging" and tumor pathology.

Induction of p16 during these highly proliferative processes is thought to be crucial for maintaining proper tissue homeostasis" Her you should cite related and recent sources referring to the role of p16 in bladder cancer and sources for aging such as: LaPak KM, Burd CE. The molecular balancing act of p16(INK4a) in cancer and aging. Mol Cancer Res. 2014 Feb;12(2):167-83. doi: 10.1158/1541-7786.MCR-13-0350. & Hasan A, Mohammed Y, Basiony M, Hanbazazh M, Samman A, Abdelaleem MF, et al. Clinico-Pathological Features and Immunohistochemical Comparison of p16, p53, and Ki-67 Expression in Muscle-Invasive and Non-Muscle-Invasive Conventional Urothelial Bladder Carcinoma. Clinics and Practice. 2023; 13(4):806-819. <https://doi.org/10.3390/clinpract13040073>

- Thank you for the suggestion. We agree and cite the paperws.

Reviewer #3:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

15. **Specific Comments to Authors:** Conclusion is that the giant stromal cells in non-tumor and tumor bladder can be used as a characteristic and relatively constant histological marker for chronic bladder damage. Likewise, according to the morphological and IHC of the mono and multinucle-ated giant cells in the bladder, they are most likely represent telocytes capable of adapting their morphology to the pathology of the organ.

- Yes, that is correct. Thank you for the note. We have revised a conclusion and emphasized on this point.

16. The manuscript is clear and presented in a well structured manner. The study is well designed. Materials and methods are described in detail. Results are reported clearly and appropriate. Tables and figures properly show the data.

The discussion is adequate with current citations. The conclusions are consistent with the evidence.

- Thank you for for the overall evaluation of our paper as good.