ANALYSIS

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The prognostic value of B-catenin, CD10 and p63 Immunohistochemical expression in urothelial carcinoma

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General Note
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ABSTRACT

Background: Detection of high-grade urothelial carcinoma is important for modification of therapy and improving the prognosis. We studied the prognostic value of β-catenin, CD10 and p63 immunohistochemical expression in urothelial carcinoma and correlated this expression with the tumor grade and stage to evaluate the prognostic value of those commonly used markers. *Material and Methods:* Eighty four cases of urinary bladder urothelial carcinoma were obtained from the pathology archive and reexamined

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histologically for diagnosis, grading and staging then stained with β-catenin, CD10, and p63 immunohistochemistry and evaluated. *Results:* Thirty cases were non invasive carcinomas and fifty four cases were invasive carcinomas. There was a significant relationship between β-catenin positivity and higher tumor stage and higher tumor grade. CD10 expression showed significant correlation with tumor grade (p=0.006) and tumor invasion. Also P63 antibody immunostaining expression revealed a significant correlation with tumor grade and tumor invasion. *Conclusion:* β-catenin, CD10 and p63 expression can be used as a prognostic factor for high grade invasive urothelial carcinoma.

Keywords: immunohistochemistry, prognosis, urothelial carcinoma

1. INTRODUCTION

Urothelial carcinoma (UC) also known as transitional cell carcinoma of the urinary bladder is considered the ninth most common cancer diagnosed worldwide (Wong et al., 2018). The bladder cancer rate is higher in Egypt than the other countries over the world (Hussien et al., 2020).

Tobacco smoking is a major risk factor for bladder cancer in addition to industrial exposure to the potential carcinogens such as aromatic amines and carbon black dust, long-term drinking of arsenic-contaminated or chlorinated water and family history of concordant cancers (Burger et al., 2013). About 80% of patients are found in the area between 50 and 80 years of age. Nearly 75-85% of urothelial carcinoma of the bladder is confined to the mucosa. On the other hand, a smaller but significant percentage of patients have advanced and muscle-infiltrative tumor at the time of diagnosis (Matalka et al., 2008).

Urothelial carcinoma prognosis is largely depending on the stage of the tumor at time of diagnosis as well as tumor histological grade (Wang et al., 2019). β-catenin protein is a subunit of the cadherin protein complex, plays an important role in cell-cell adhesion and gene transcription. During tumorigenesis, when E-cadherin expression on cell surface is decreased or when proteasomal degradation of the cytosolic β-catenin is inhibited, β-catenin accumulates in cytoplasm and then migrates into the nucleus. Interaction between β-catenin in the nucleus and downstream transcription factors cause abnormal activations of downstream genes (Kraus et al., 1994).

Mutations and overexpression of β-catenin gene are associated with a poor prognosis in many cancers, such as breast carcinoma, hepatocellular carcinoma and colorectal cancer. Many reports indicate that β-catenin acts as a Wnt/ Wg signal transducer in cancer development (McCubrey et al., 2016). CD10 is a surface zinc-dependent enzyme metalloprotease that inactivates various bioactive neuropeptides (Bahadir et al., 2009). p63 is substantially expressed in the basal cell layers of epithelial tissues, including skin, urothelium, prostate and breast, so p63 is used as a myoepithelial marker (Westfall et al., 2004). In this study we evaluated β-catenin, CD10 and p63 immunohistochemical expression in both noninvasive and muscle-invasive urothelial carcinoma and correlated this expression with various histopathological parameters including tumor grade and tumor pathological stage.

2. MATERIAL AND METHODS

A total of 84 formalin-fixed paraffin-embedded urinary bladder transurethral resection (TUR) biopsies of urothelial carcinomas covering the period from March 2015 to March 2018 were retrieved from the archival materials of the histopathology department of Al-Azhar university hospitals. The pathology request forms usually include the patient demographic data and brief clinical data (Kohail, 2019) and must be accompanied each patient specimens transformed to the histopathology lab (Hasan et al., 2020a). So all the clinic-pathological data were obtained from the available surgical pathology requests and reports included age, sex, tumor grade and tumor stage (Figure1).

All hematoxylin and eosin (H&E) stained sections were reviewed regarding tumor grade based on the WHO 2016 criteria (Humphrey et al., 2016) and tumor stage according to American Joint Committee on Cancer guidelines (Gershenwald et al., 2017).

From each paraffin block, 4 sections of 4 µm thickness were taken. One section was stained with H&E for revision of the histopathological diagnosis and the other 3 sections were stained immunohistochemically using the streptavidin–biotin alkaline phosphatase method for monoclonal antibodies: β-catenin monoclonal antibody (Dako, Concentrate, code IR702 Carpinteria, CA 93013 USA) and for positive control sections from normal colonic mucosa were used. p63 monoclonal antibody (Dako, Concentrate, catalog M7247 Carpinteria, CA 93013 USA) and for positive control, sections from normal prostate were stained for p63. CD10 specific monoclonal antibody (Dako, Concentrate, catalog M7308, Carpinteria, CA 93013 USA) and for positive control, sections from normal liver were stained for CD10.

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Evaluation of staining

Assessment of β-catenin antibody immunostaining

For β-catenin antibody, membranous and cytoplasmic staining was scored according to the method described by Serkan et al. in 2015 (Senol et al., 2015), Percentage of tumor-cell positivity as follow: Score 0 (0-5%), +1 (6-25%), +2 (26%-50% and score +3 (more than 50%). Staining intensity from 1 to 3 (1= weak, 2= moderate, 3= strong). The percentage product of the positive cells and the staining intensity was divided by 3, making the reactivity score ranging from 0 to 100. Negativity is recorded when the reactivity score is up to 10%, 10% to 50% is weakly positive and strongly positive if it is 50% to 100%.

Assessment of CD10 antibody Immunostaining

According to Mohammed et al. in 2013: Brown staining of the cell membrane and/or cytoplasm by CD10 was considered positive, with a 5% cut-off point in tumor cells, The extent of immunoreactivity was scored according to the following criteria: (Negative): <5% positive cells.(+1): 5%-50% positive cells.(+2): >50% positive cells by counting the maximum number of stained cells (1000 cells) in 10 high-power spots (Mohammed et al., 2013).

Assessment of P63 antibody immunostaining

According to Reis-Filho., et al. in 2002: A semi-quantitative assessment of p63 expression was performed, according to the following criteria: (0) negative nuclear staining of neoplastic cells. (+1) weak (= 0-5% positivity) of neoplastic cells. (+2) moderate (5- 50% positivity) of neoplastic cells. (+3) diffuse more than (50% positivity) of the neoplastic cells (Reis-Filho., et al., 2002).

Statistical Analysis

SPSS version 19 (SPSS Inc., Cary, NC) was used for the statistical analysis. Descriptive analysis was used including mean ±standard deviation (SD) for quantitative data and frequency tables for qualitative data. Independent sample T-test was used for comparing the difference of means in quantitative data, whereas Chi square test was used for the qualitative data.

3. RESULTS

Demographic data

Clinicopathologic data of 84 cases of urinary bladder urothelial carcinoma were obtained from the patient`s medical files and pathology reports. Analysis of these data showed male predominance (62/ 84) (73.8%), female cases counted 22/ 84 (26.2%). The age of patients ranged from 32 to 88 years (mean age 56.5).

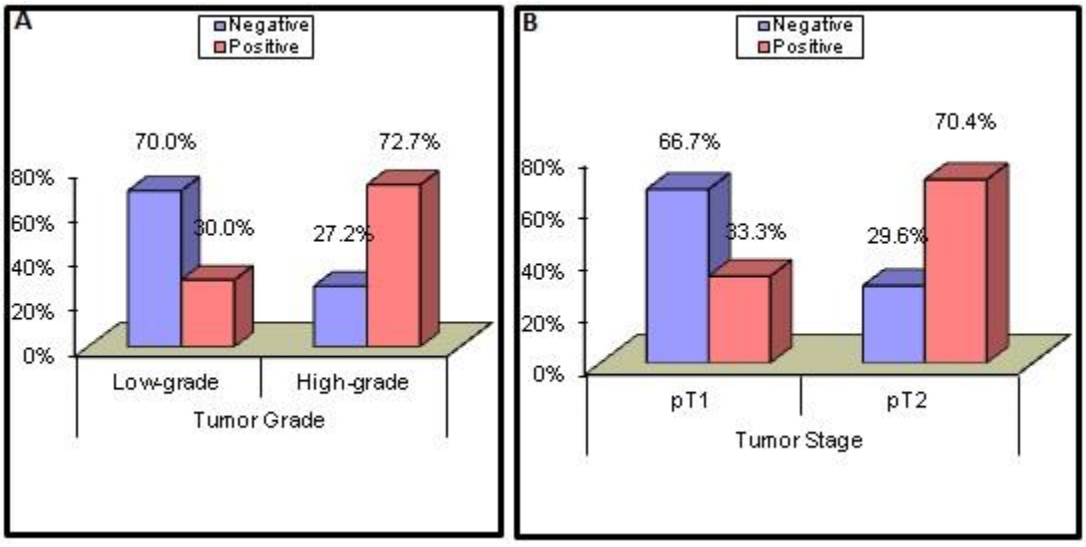

Figure 1: a bar chart showing the percentage of tumor grade and stage of the studies cases

Histopathological findings

The collected 84 cases of bladder urothelial carcinomas showed 30/84 cases (35.7%) of non-muscle invasive urothelial carcinoma (Figure 2A) were divided into 8/84 cases (9.5%) high grade non invasive tumors and 22/84 cases (26.2%) low grade non invasive tumors.

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Fifty four out of 84 (64.3%) cases were muscle invasive urothelial carcinoma (Figure 2B) with 36/84 (42.9%) cases were high grade invasive tumor and 9/42 cases (21.4%) were low grade invasive tumor.

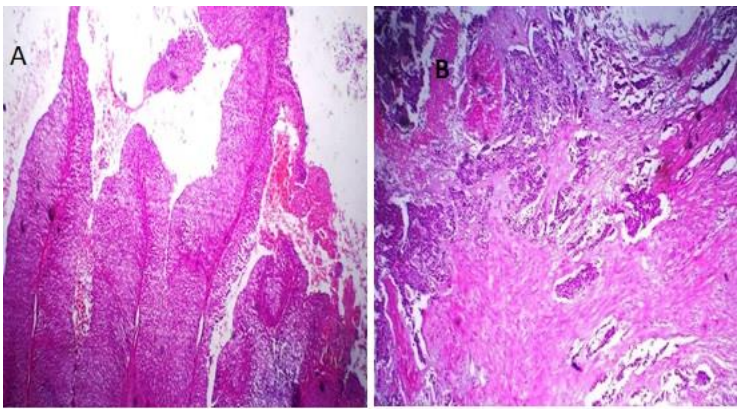

Figure 2: A) Low Grade Urothelial carcinoma T1, (H&E X100). B) High Grade muscle invasive Urothelial carcinoma T2 (H & E X100)

Immunohistochemical findings

β-catenin antibody immunostaining of the all low grade cases showed 28/40 (70%) negative stainining, 8/40 (20%) cases are weakly positive (Figure 3A) and 4/40 (10%) cases are positive. On the other hand, as regarding high grade cases of urothelial carcinoma 20/44 (45%) cases are negative, 10/44 (23%) cases are weakly positive and 14/44 (32%) cases are strong positive (Figure 3B).

Regarding tumor stage β-catenin antibody immunostaining of 30 urothelial carcinoma stage pT1 showed 18/30 (60%) negatively stained cases, 6/30 (20%) weakly positive and 6/30 (20%) cases are positive. On the other hand, as regarding pT2 stage; 18/54 (33.3%) cases show negative staining, 12/54 (22.3%) cases are weakly positive and 24/54 (44.4%) cases are positive.

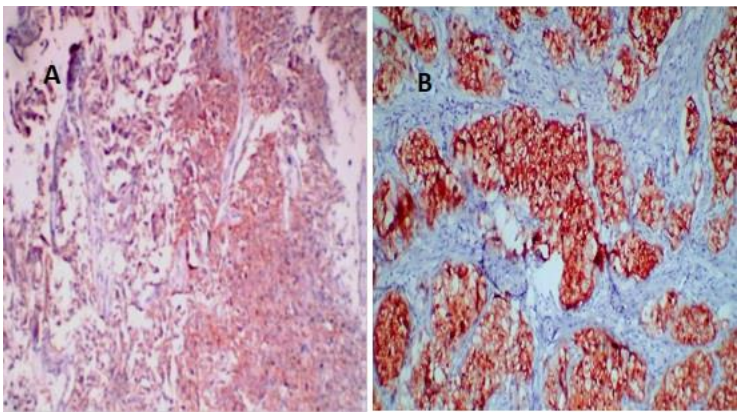

Figure 3: A) A case of low grade, pT1 urothelial carcinoma showing weak positivity to β-catenin antibody Immunostaining. B) A case of high grade, pT2 urothelial carcinoma showing strong positivity to β-catenin antibody Immunostaining.

There was a significant relationship between β-catenin positivity and higher tumor stage (T2) (p =0.025) and higher tumor grade (p = 0.011) (Table 1).

CD10 immunostaining was predominantly cytoplasmic (Figure 4A), some cases showed also cytoplasmic and membranous staining (Figure 4B).

CD10 antibody immunostaining of the 40 low grade cases showed; 28/40 (70%) cases are negative, 10/40 (25%) cases are weakly positive and 2/40 (5%) cases are positive. On the other hand, as regarding high grade cases; 12/44 (27%) cases are negative, 12/44 (27%) cases are weakly positive and 20/44 (46%) cases are positive.

For tumor stage; CD10 immunostaining showed 20/30 (67%) pT1 cases are negative, 6/30 (20%) cases are weakly positive and 4/30 (13%) cases are positive. Stage pT2 cases showed 16/54 (30%) negative staining cases, 12/54 (22%) weakly positive cases and 26/54 (48%) positive staining cases.

As a result, CD10 expression showed significant correlation with tumor grade (p=0.006) and tumor invasion (p=0.020) (Table 2).

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p63 antibody immunostaining showed 0/20 (0%) negatively stained low grade cases, 3/20 (15%) cases are +1, 5/20 (25%) cases are +2 and 12/20 (60%) cases are +3 positive staining (Figure 5A). On the other hand, as regarding high grade cases of urothelial carcinoma 12/44 (27%) cases are negative, 14/44 (32%) cases are +1, 10/44 (23%) cases are +2 (Figure 5B) and 8/44 (18%) cases are +3.

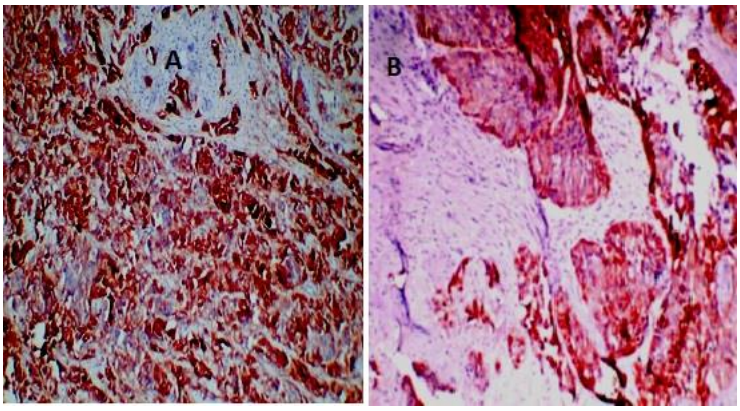

Figure 4: A) A case of high grade urothelial carcinoma showing strong cytoplasmic positivity to CD10antibody Immunostaining. B)A case of high grade pT2 urothelial carcinoma showing strong cytoplasmic& membranous positivity to CD10antibody Immunostaining.

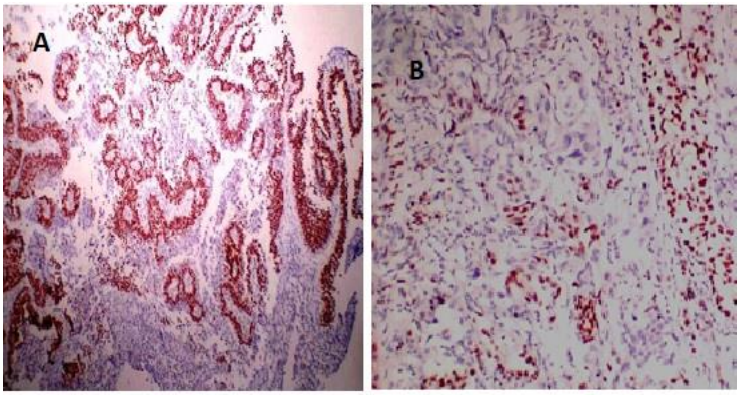

Figure 5: A) A case of low grade PT1 urothelial carcinoma showing strong nuclear positivity to p63 antibody Immunostaining B)A case of high grade urothelial carcinoma showing moderate positivity to p63 antibody Immunostaining.

Regarding tumor stage; P63 showed 0/30 (0%) cases with negative staining, 4/30 (13%) cases are +1, 8/30 (27%) cases are +2 and 18/30 (60%) cases are +3. On the other hand, as regarding pT2 cases of urothelial carcinoma 14/54 (26%) cases are negative, 16/54 (30%) cases are +1, 14/54 (26%) cases are +2 and 10/54 (19%) cases are +3. P63 antibody immunostaining expression revealed a significant correlation with tumor grade (p=0.012) and tumor invasion (p=0.031) (Table 3).

Table 1: β-catenin antibody Immunostaining

		β-catenin antibody Immunostaining				Chi-square test	
		Negative	**Weak Positive**	**Positive**	**Total**	**X^2**	**P-value**
Grade No.42	**Low-grade**	14(70%)	4(20%)	2(10%)	20(47.6%)	6.461	0.011
	High-grade	10(45.5%)	5(22.7%)	7(31.8%)	22(52.4%)		
Stage No.42	**pT1**	9(60%)	3(20%)	3(20%)	15(35.7%)	5.060	0.025
	pT2	9(33.3%)	6(22.2%)	12(44.4%)	27(64.3%)		

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Table 2: CD10 antibody Immunostaining results

		CD10 antibody Immunostaining				Chi-square test	
		Negative	Weak Positive (+1)	Strong Positive (+2)	Total	X^2	P-value
Tumor Grade	Low-grade	14(93.3%)	5(33.3%)	1(6.7%)	20(47.6%)	7.668	0.006
	High-grade	6(22.2%)	6(22.2%)	10(37.0%)	22(52.4%)		
Tumor Stage	pT1	10(66.7%)	3(20.0%)	2(13.3%)	15(35.7%)	5.401	0.020
	pT2	8(29.6%)	6(22.2%)	13(48.1%)	27(64.3%)		

Table 3: P63 antibody Immunostaining results

		P63 antibody Immunostaining					Chi-square test	
		Negative	+	++	+++	Total	X^2	P-value
Tumor Grade	Low-grade	0(0%)	3(15%)	5(25%)	12(60%)	20(47.6%)	6.364	0.012
	High-grade	6(27.3%)	7(31.8%)	5(22.7%)	4(18.2%)	22(52.4%)		
Tumor Stage	pT1	0(0%)	2(13.3%)	4(26.7%)	9(60%)	15(35.7%)	4.667	0.031
	pT2	7(25.9%)	8(29.6%)	7(25.9%)	5(18.5%)	27(64.3%)		

4. DISCUSSION

Bladder carcinoma, Transitional Cell Carcinoma, is common, taking the fourth position on the list of the most frequent cancers in men and the ninth position in women (Siegel et al., 2012).

Male predominance is reported in this study as well as the previous studies in Egypt (Khaled, 2005; Moussa et al., 2019) and other countries (Band et al., 2005). The mean age of this tumor is around 60 years (Moussa et al., 2019; Fedewa et al., 2009); we recorded in this study a little lower mean age (56.5).

The real UC danger is in the frequent recurrence, mortality rate and transition from non-invasive to an invasive tumor. Despite advances in diagnostic tools and therapeutic techniques, Urinary bladder cancer outcomes have obviously remained unchanged (Hussien et al., 2020).

The management of bladder tumors still depends on the pathologic staging, which might not reflect the actual risk for the patient. Therefore, assessing molecular alterations for individual tumors offers detection of the cellular pathway that is deregulated in bladder tumorigenesis process and progression (Zlatev et al., 2015).

β-catenin functions as part of the E-cadherin/β-catenin complex and plays a role in cell-to-cell adhesion. The Wnt/β-catenin pathways have been reported to regulate urothelial homeostasis and carcinogenesis (Huang et al., 2018).

We found that β-catenin antibody showed negative immunostaining in 70% of low grade cases and only 30% of cases were positive. On the other hand, the high grade cases of urothelial carcinoma showed negativity in 45% cases and 55% cases were positive. Regarding tumor stage β-catenin antibody immunostaining showed that 60% of non-muscle invasive cases were negative and only 40% positive cases. On the other hand, only 30% of the invasive (pT2) cases were negative and the rest 70% were positive.

So, there is a significant relationship between β-catenin positivity and tumor stage and high-grade bladder carcinoma ($p < 0.01$), this result appears as the same of previous studies (Senol et al., 2015 , Del Muro et al., 2000) and a recent study reporting a significant β-catenin reduction associated with high tumor grade and muscle invasive tumors (Moussa et al, 2019).

CD10 is a surface zinc-dependent enzyme metalloprotease that inactivates various bioactive neuropeptides (Bahadir et al., 2009). In addition to its enzymatic function, CD10 protein has a direct role in signal transduction pathways that regulate cell growth and apoptosis and due to its structural similarity to matrix metalloproteases in the stroma, CD10 may affect invasion and metastatic potential of the tumor cells by altering the cellular microenvironment (Iwaya et al., 2002). CD10 function in urothelial carcinoma remains controversial. Kumagai-Togash et al. concluded that high tumorous CD10 is significantly associated with poorer prognosis and higher tumor grade, stage and vessel infiltration (Kumagai-Togashi et al., 2019). Some other similar studies are consistent with our recorded results (Bahadir et al., 2009; Mohammed et al., 2013; Murali and Delprado, 2005).

p63 gene, a homologue of the p53 tumor suppressor gene. Since mutations of the p63 gene in human cancer are rare, its biofunction may include tumor suppression and oncogenic activity in various cancer types. Unlike the tumor suppressor protein p53, which is only detectable in epithelial cells under stress conditions, p63 is expressed in the nuclei of mature epithelial cells in the basal layer under normal conditions and is overexpressed in many cancers including the urothelial carcinoma (Urist et al., 2002;

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Hasan et al., 2020b). In this study; p63 antibody immunostaining showed positive reaction in all pT1 stage cases (100%), while pT2 cases showed 26% negatively stained cases and 74% cases with positive reaction which means that p63 expression revealed significant reduction in high grade and high stage cases. This result is in agreement with other two studies performed in 2014 and 2019 (Lin et al., 2014; Moussa et al., 2019).

5. CONCLUSION

β-catenin, CD10 and p63, immunohistochemical expression in urothelial carcinoma of the urinary bladder shows significant correlation with tumor grade and stage and may be used as prognostic predictors of the urothelial carcinoma of the urinary bladder. It is not the only study for evaluation of the prognostic value of β-catenin, CD10 or p63, but according to our knowledge it is the first study for the three markers with each other and we recommend using the three markers to get both diagnostic and prognostic clinical benefits, also more studies on other potential prognostic factors should be encouraged.

Author Contributions

AH: manuscript design, histopathology and immunohistochemical interpretation, manuscript preparation and final revision

R E: study concept, material collection, histopathology and immunohistochemical interpretation, manuscript preparation, editing and revision

N O: statistical analysis, histopathology and immunohistochemical interpretation, manuscript preparation and writing.

E M: data collection, histopathology material collection and examination, literature search.

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This study has not received any external funding.

Conflict of interest

The authors declare that there are no conflicts of interests.

Ethical approval

No human or experimental subjects in this study, a local ethical approval is provided.

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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