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Evaluation of Hexokinase 2 and Serum LDH in B-cell Non-Hodgkin's Lymphoma Patients

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ABSTRACT

Background and Objective: Tumor cells produce energy by glycolysis and Lactate Dehydrogenase and Hexokinase are the key part of glycolysis, The present study aimed to evaluate the expression of Hexokinase 2 and serum LDH in B-cell Non-Hodgkin's Lymphoma patients

Method: A total of 84 B-cell Non-Hodgkin's Lymphoma Patients were enrolled in the study. HK-2 Marker was studied by Immunohistochemistry and LDH analysis was done by Cobas 6000 analyser method and correlated with Clinico-Pathological Parameters and Diagnostic panel.

RESULT:73% of B-cell NHL patients had Abnormal LDH. It was significantly correlated with Multiple Disease site (P=0.002). In correlation with Diagnostic Panel (MIb1, CD10, CD2, MUM1, BCL6, BCL2) a higher trend of Abnormal LDH was seen in BCL-6 positive and BCL-2 negative Patients. 64% of patients had HK-2 expression. In correlation with Clinical parameters, it was significantly correlated with >50 age group, while in correlation with pathological parameters A significant correlation observed with single disease site as compared to multiple disease site (P=0.004), In correlation with Diagnostic panel A higher trend of HK-2 Expression was observed in CD10 Negative and BCL-2 Negative Patients. Further Univariate survival analysis of LDH and HK-2 showed similar Overall survival in Abnormal and normal LDH level patients and HK-2 Positive and negative Patients respectively. Further Intercorrelation of both markers, showed almost similar expression of HK-2 between patients with normal LDH level and abnormal LDH level.

CONCLUSION: Abnormal LDH level was closely associated with patients having disease at multiple sites, suggesting its activity to be associated with the advancement of the disease, HK-2 positivity was related with older age group, strengthens the findings of increased altered metabolic activity with older age, They are also associated with BCL-2 negativity that indicates that anti-apoptotic activity of BCL-2 might be responsible for that Though there was no significant correlation of LDH,, HK-2 with overall survival, majority of the patients who were dead had abnormal LDH and half of them showed positive HK-2 expression

Briefly our data indicates that LDH and HK-2 can be useful parameter in defining clinical and prognostic aspects in NHL patient but needs further evaluation with larger groups of patients

Key words: NHL, Altered metabolism, Hexokinase, LDH

INTRODUCTION

Lymphomas are heterogeneous group of malignancy arising from Lymphocytes includes T cell and B cell, among which B

cell lymphomas are most common. According to hospital based registry of Gujarat Cancer & Research Institute, approximately 3.3% of Lymphoma cases have been registered [1]

Among various risk factors of cancer like older age, family history, weak immune system etc., altered metabolism is also one of the causes of cancer. The relationship between Cancer and altered cellular metabolism has been deciphered decades ago by Otto Warburg. He reported that tumors showed unusually high rates of glucose uptake and lactate production compared with normal tissues even in the presence of oxygen. This Glycolysis produces ATP with lower efficiency, but at a faster rate than oxidative phosphorylation. This faster rate of ATP production is thought to aid the rapid proliferation of cancer cells. In addition to providing ATP, the high glycolytic rate may favor the growth of cancer cells through increasing biosynthesis of important molecules such as lipids, nucleotides, NADPH and amino acids. Other metabolic products of glycolysis, such as lactate and H+, cause a consistent acidification of the extracellular environment and favor cancer invasion Lactate Dehydrogenase (LDH) and Hexokinase 2 (HK-2) are the important enzyme which plays a role in the process of Glycolysis. [2,3]

LDH is an enzyme that catalyzes the conversion of lactate to pyruvate using NAD+ as a cofactor and located in cytosol and also present in mitochondria, it is closely related to malignant bio-characteristics of cancer via various mechanisms like, it can promote cancer cell proliferation and maintain cell survival, enhance cancer cell invasion and metastasis, angiogenesis and it can also assist cancer cells in immune escape [4,5,6,7,8,9]

Hexokinase is an initial enzyme of glycolysis, catalyzing phosphorylation of glucose. There are four isoforms of Hexokinase HK1, HK2, HK3, HK4 among them HK-2 has a 100-fold higher affinity for glucose than others and it is localized either free in cytosol or bound to mitochondrial outer membrane, HK-2 is the predominant isoform which over expressed in cancer cell [10]

However, little is known about the association of LDH level and HK-2 expression in Non-Hodgkin's lymphoma cancer. So, in the present study, we aimed to reveal possible relation of these enzymes and Non-Hodgkin's Lymphoma patients.

MATERIALS AND METHOD

In this retrospective study, 84 (DLBCL, Follicular Lymphoma, Marginal Zone type and Burkitt's Lymphoma) Non-Hodgkin's Lymphoma patients who had been diagnosed and treated at GC&RI in the duration of 2016 to 2017 were included. The detailed clinical history such as patient's age, gender, habit (smoking or tobacco), histopathological finding, and treatment offered and disease status were recorded in the division from the case file maintained at the Institutional Medical Record Department. Paraffin embedded tissue block of these NHL patients were archived from Histopathology Department of GCRI. The study was approved by the Institutional Scientific Review Board and Ethics Committee.

METHODOLOGY

Immunohistochemical localization HK-2 was evaluated on formalin fixed paraffin embedded (FFPE) tissue blocks containing primary tumor evaluated by Hematoxylin and Eosin (H&E) staining, on Ventana Benchmark XT autoimmunostainer using Ventana reagents (Ventana, USA). The commercially available antibodies used were HK-2 (Clone H.738, Thermo Scientific. 1:50). Briefly, 3-4 µm thin sections were cut on microtome (Leica, Germany) and taken on to 3-Aminopropyltriethoxysilane (APES) coated slides. Briefly the protocol included following steps of deparaffinization using EZ prep solution, antigen retrieval for 60 minutes using retrieval solution CC1 and incubation with ultra view DAB inhibitor

for 4 minutes, addition of 100µL of HK-II antibody at 37ºC for 48 minutes, followed by incubation with ultra view HRP multimer for 8 minutes, ultra view DAB Detection kit for 8 minutes. The sections were counterstained with Hematoxylin for 8 minutes and bluing reagent for 4 minutes and mounted with DPX.

Evaluation of Serum LDH

Evaluation of Lactate Dehydrogenase in human serum was done on Roche/Hitachi Cobas C systems: Serum collected using standard sampling tubes. Reagents were ready to use and packed in closed cassettes which made reagent handling fully automated. This method has been standardized against the original IFCC formulation using Deionized water as zero calibration pipettes together with a manual photometer providing absolute values and the substrate-specific absorptivity. The COBAS 6000 system automatically calculated the LDH activity of each sample.

Scoring

Two individual observers scored the sections. Cytoplasmic staining pattern for HK-2 was observed. The staining was scored as weak, moderate and strong positive. For analysis, weak, moderate and strong positive were scored as positive and cells with no cytoplasmic staining were scored as negative.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS statistical software version 20 (SPSS Inc, USA). Mean, Standard error (SE) of mean and median were calculated and Pearson's Chi-square test with Pearson's correlation coefficient (r) was used to assess correlation and significance between two parameters. Univariate survival analysis was carried out by Kaplan Meier and Log Rank statistics was used to assess the prognostic significance of Overall Survival (OS). P values $\leq$ 0.05 were considered to be significant.

RESULTS

Patient's Characteristics:

In the present study 84 Non Hodgkin's Lymphoma patients were included. The median age was 50 years and was used as cut off. Out of 84 patients, (57%, 48/84) of the patients, were of $\leq$ 50 years, whereas (43%, 36/84) had >50 years of age. (61%,51/84) patients were male and (39%,33/84) patients were female, (19%, 16/84) were Habituated (Tobacco chewing/ Smoking), and (81%, 61/84) were non-habituated.

In relation to pathological parameters (71%, 40/84) patients had high grade tumour whereas (29%,16/84) patients had lower grade tumour and there were 28 patients in whom tumour grade was not defined. In relation to Histological subtypes (73%, 61/84) patients were of DLBCL subtype, (17%, 14/84) were of Follicular Subtype, (6%, 5/84) were Marginal zone and (5%, 4/84) patients were of Burkitt's subtype. Disease sites were defined as single site where only one site was involved included Lymph Node involvement at Axilla, Abdomen-Pelvis, Cervical, Tonsil, Inguinal region, Neck & brain, GE junction, Supraclavicular region, Eye Lid, and liver (21%, 18/84), whereas (79%, 66/84) of patients had disease at multiple sites, where in Lymph nodes at two or more sites were involved (Table 1).

The patients were treated with different regimen, where in 48% (N=40/84) of the patients were treated with R+Chop (Rituximab + Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Vincristine (Oncovin), 27% (N=23/84) were treated with R+CHOP+CT (Cisplatin, Gemcitabine, methotrexate, oxaliplatin, capecitabine and DHAP), 14% (N=12/84) of the patients were treated with CHOP alone, whereas 7%(N=6/84) were treated with Rituximab and 4% (N=3/84) were treated with other chemotherapeutic drugs like Leucovorin, Cytarabine, Filgrastim, etc. The Maximum Follow-up period was 120 months with a median follow-up was 28 months.

Table 1: Patients Clinicopathological Characteristic

Clinicopathological Characteristic	No of patients	%
Age(Years)		
≤50	48	57%
>50	36	43%
Gender		
Male	51	61%
Female	33	39%
Habit		
Habituated	16	19%
Non-Habituated	68	81%
Tumor grade		
High grade	40	71%
Low grade	16	29%
Histological subtype		
DLBCL	61	73%
Follicular	14	17%
Marginal Zone	5	6%
Burkitt's	4	4%
Disease site		
Single site	18	21%
Multiple site	66	79%

Correlation between LDH and Diagnostic Lymphoma Panel:

Further, correlation was performed between LDH Diagnostic Panel for B cell Non-Hodgkin's Lymphoma that included MIB1, CD2, CD10, MUM1, BCL-6, BCL-2. No significant correlation of LDH was noted with these markers included in the panel. However, higher level of abnormal LDH was observed in BCL-6 positive (76%, 28/37) and BCL-2 negative patients (86%, 12/14) as compared to their respective counterparts (Table 3).

LDH expression:

Out of 84 patients (73%, 61/80) patients showed (>190IU/L) abnormal LDH level while (27%, 23/80) patients showed Normal (Normal range 100-190u/l) LDH level.

Correlation between LDH and Clinicopathological parameters

All the patients classified into series of subgroups according to different clinicopathological factors and the potential correlation between these factors and serum LDH level was analysed. No, significant correlation with clinical parameters was noted. In, relation with pathological parameters a significant correlation was noted with multiple disease site, where in a significant higher expression of abnormal LDH was noted in patients having disease at multiple disease site (80%,53/61) as compared to patients having disease at single site (44%,8/61,P=0.002), No, significant association was noted between the LDH and other pathological parameters (Table 2).

Table 2: Correlation of LDH and Hexokinase II with clinicopathological parameters

Parameter	Normal LDH N(%)	Abnormal LDH N(%)	P	Hexokinase Negative N(%)	Hexokinase Positive N(%)	P
Total	23(27%)	61(73%)		28(36%)	50(64%)	
Age (Years)			0.120			0.021
≤50	10(21%)	38(79%)		21(47%)	24(53%)	
>50	13(36%)	23(64%)		7(21%)	26(79%)	
Gender			0.325			0.367
Male	12(23%)	39(77%)		15(32%)	32(68%)	
Female	11(33%)	22(67%)		13(42%)	18(58%)	
Habit			0.390			0.818
Habituated	3(19%)	13(81%)		5(33%)	10(67%)	
Non Habituated	20(29%)	48(71%)		23(37%)	40(63%)	
Grade			0.841			0.611
High Grade	9(22%)	31(78%)		16(42%)	22(58%)	
Low Grade	4(25%)	12(75%)		7(50%)	7(50%)	
Histological Subtypes			0.98			0.254
DLBCL	17(28%)	44(72%)		18(32%)	39(68%)	
Folicular	4(29%)	10(71%)		7(54%)	6(46%)	
Marginal Zone	1(20%)	4(80%)		1(20%)	4(80%)	
Burkitt's	1(25%)	3(75%)		2(68%)	1(33%)	
Disease site			0.002			0.003
Multiple site	13(20%)	53(80%)		13(21%)	48(79%)	
Single site	10(56%)	8(44%)		10(59%)	7(41%)	

Correlation between LDH and Diagnostic Lymphoma Panel:

Further, correlation was performed between LDH Diagnostic Panel for B cell Non-Hodgkin's Lymphoma that included MIB1, CD2, CD10, MUM1, BCL-6, BCL-2. No significant correlation of LDH was noted with these markers included in the panel. However, higher level of abnormal LDH was observed in BCL-6 positive (76%, 28/37) and BCL-2 negative patients (86%, 12/14) as compared to their respective counterparts (Table 3).

Table 3: Correlation of LDH and Hexokinase 2 with Diagnostic Panel

Parameter	Normal LDH N(%)	Abnormal LDH N(%)	P	Hexokinase 2 Negative N(%)	Hexokinase 2 Positive N(%)	P
MIb 1			0.947			0.243
≤70	12(29%)	29(71%)		15(41%)	22(59%)	
>70	10(29%)	25(71%)		9(27%)	24(73%)	
CD10			0.394			0.066
Positive	12(30%)	28(70%)		18(47%)	20(53%)	
Negative	7(21%)	26(79%)		8(26%)	23(74%)	
CD2			0.505			0.545
Positive	4(36%)	7(64%)		4(36%)	7(64%)	
Negative	8(26%)	23(74%)		8(27%)	22(73%)	
MUM1			0.624			0.273
Positive	6(23%)	20(77%)		8(31%)	18(69%)	
Negative	7(29%)	17(71%)		11(46%)	13(54%)	
BCL6			0.323			0.610
Positive	9(24%)	28(76%)		11(31%)	24(69%)	
Negative	8(36%)	14(64%)		3(38%)	13(62%)	
BCL2			0.239			0.243
Positive	11(31%)	25(69%)		15(44%)	19(56%)	
Negative	2(14%)	12(86%)		3(25%)	9(75%)	

Hexokinase 2 expression:

Out of 84 patients, (64%, 50/84) showed cytoplasmic expression of HK-2 (Figure 1) while (36%, 28/84) were negative for HK-2 expression (Figure 2)

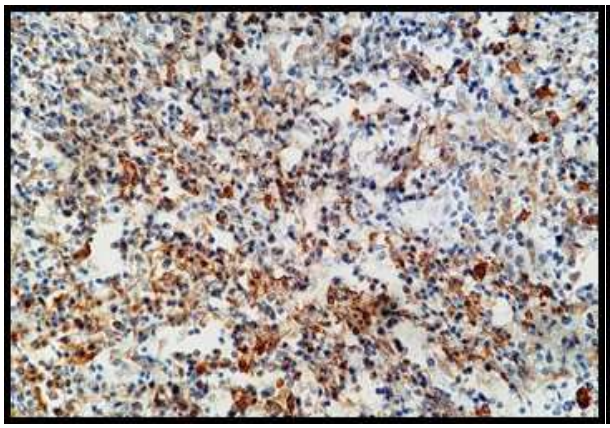

Figure 1: Positive staining for Hexokinase 2 expression in Non-Hodgkin's Lymphoma patients

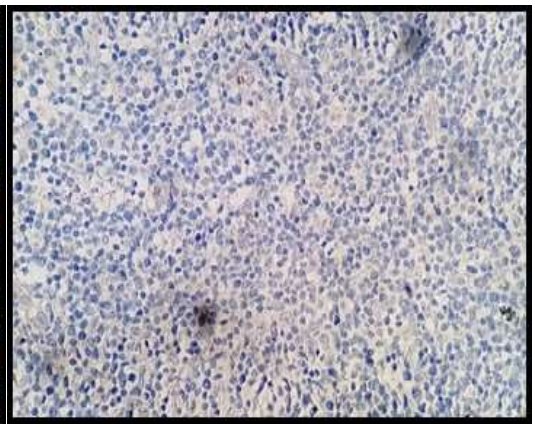

Figure 2: Negative Staining for Hexokinase 2 expression in Non-Hodgkin's Lymphoma patients

Correlation between HK-2 and Clinico pathological parameter:

Further, in correlation of HK-2 a significant higher HK-2 expression was noted in patients with >50 years age (79%, 26/33) as compared to patients with ≤50 (53%, 24/45) years of age (P=0.021). In correlation with pathological parameter significant higher was expression was noted in patients with multiple disease site (79%, 48/61) as compared to those having single disease site (41%, 7/17, P=0.003). No significant

correlation was noted with other parameters (Table 2).

Correlation between HK-2 and Diagnostic Lymphoma Panel:

In correlation of HK-2 with Diagnostic panel (Mib1, CD5, CD10, MUM1, BCL-6, BCL-2) a trend of higher HK-2 expression was noted in CD10 negative (74%, 23/31) and BCL-2 negative (75%, 9/12) patients, compared to their respective counterparts. No, significant correlation was noted with other markers included in the panel (Table 3).

Inter correlation between HK-2 and LDH

No significant correlation between HK-2 and LDHwas noted as similar expression of HK-2 was noted between in patients with normal LDH level and abnormal LDH level patients (Table4)

Table 4: Intercorrelation between LDH and HK-2

Parameters	Hexokinase Negative N(%)	Hexokinase Positive N(%)	P
LDH			0.638
Normal	7(32%)	15(68%)	
Abnormal	21(38%)	35(62%)	

Univariate Survival analysis

Disease free survival was not evaluated as 66 out of 84 patients had persistent disease and hence comparable data could not be achieved.

According to Kaplan-Meier Univariate survival analysis, with respect to Overall survival (OS), similar incidence of death was noted in patients with normal and abnormal LDH level (Figure 3a)

Also, no significant difference in Overall Survival was noted with HK-2 expression as similar incidence of death was observed showingHK-2 Positive and Negative expression (Figure3b).

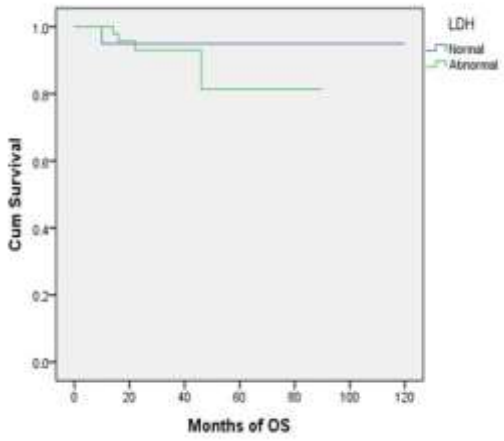

Figure 3a: Kaplan-Meier Survival analysis Overall Survival (OS) for LDH in Non-Hodgkin's Lymphoma patients:

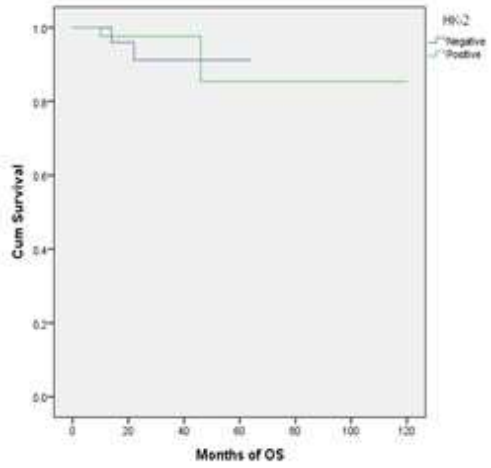

Figure 3b: Kaplan-Meier Survival analysis for Overall Survival (OS) for HK-2 in Non-Hodgkin's Lymphoma patients

Abnormal LDH and HK-2 expression in dead patients

However, when the LDH level of dead patient was seen, 5/6 patients had abnormal LDH level and also 3/6 patients were positive for HK-2. These patients were treated with Rituximab + CHOP suggesting that abnormal LDH and HK-2 may be associated with treatment resistance but needs to be evaluated in a larger group.

DISCUSSION

Lymphomas are a diverse group of malignancies arising from Lymphocytes, The International NHL Prognostic Factors Project developed a predictive model and determined five factors: Age, Tumour, stage, Serum concentration of Lactate Dehydrogenase (LDH), performance status, and number of sites of Extra nodal disease as the International Prognostic Index (IPI). Among them, LDH plays an important role

in Altered Metabolism and is one of the major causes which induce various types of cancers including NHL.[11] Enzymes like LDH and HK are released by tumour cells, due to intracellular machinery alteration and apoptosis deregulation. The mechanism of altered metabolism was first explained by Otto Warburg [12]

In this retrospective study pre-treatment LDH levels were evaluated on Cobas 6000 analyzer. 73% of the patients showed (>190 IU/L) abnormal LDH level, while 27% patients showed normal (Normal range 100-190 IU/L) LDH level, Similar results were observed by Rama Mani et.al in his study in NHL patients [13]

In the present study, no significant correlation of LDH was observed with Clinical Parameters age, gender and habit. The findings were in accordance with different study groups in various malignancies.[14,15,16,17] With pathological parameters, a significant correlation of abnormal LDH was noted in patients having disease at multiple sites as compared to those having disease at a single site (P=0.002). The results were comparable with the study of W. Gui et.al in NHL[18] Higher, expression at Multiple site indicates the probable increase in altered metabolic activity with the progression of the disease. No significant correlation was noted with Tumor grade and Histological subtypes. Further, LDH expression was then correlated with Diagnostic Panel (MIB1, CD10, CD2, MUM1, BCL6, and BCL2) of NHL. Higher, Abnormal LDH level was observed in BCL-6 positive and BCL-2 negative patients. The results were in concordance with studies in NHL and CML respectively by[20,21] he results were in discordance with study of Hanan et.al; 2011 who showed higher LDH in BCL-2 positive in NHL, and no significant correlation with other markers.[22] Disease free survival was not evaluated as 79 % of the patients had persistent disease. In relation with Overall Survival (OS) similar incidence of death was observed in patients with abnormal and normal LDH level.

Further, HK-2 was evaluated where in 64% patients were positive for HK-2 expression and 36% were negative for HK-2 expression. Similar results were observed by other study groups in various malignancies [23,24]

When HK-2 expression was correlated with clinical parameters, in correlation with age a significant higher HK-2 expression was noted in patients with >50 years of age as compared to patients with ≤ 50 years of age (p=0.021), Higher positive expression of HK-2, in patients with older age group signifies that alteration in metabolism increases with age. No significant correlation was noted with gender and habit. In Correlation of HK 2 with disease site a significant higher HK-2 expression noted in patients having disease in multiple sites as compared to patients having disease at single site (p=0.004). The results were in discordance with that of were noted by J.A. Ferry et.al in Lymphoma[25] No significant correlation was noted with other parameters, however with histological subtypes, higher HK 2 was noted in Marginal Zone subtype followed by DLBCL subtype, Follicular subtype and Burkitt's subtype, The results were comparable to the study of Martin et.al in NHL[26] Further, When HK-2 was correlated with Diagnostic panel markers (MIb1, CD10, CD2, MUM1, BCL6 and BCL2) higher HK-2 expression was observed in CD10 negative and BCL-2 negative patient. The results were similar to another study in Gastric Carcinoma[27] The anti-apoptotic activity of Bcl2 might be responsible for this but needs to be evaluated further in a larger cohort. In relation with Overall Survival (OS), similar incidence of death was observed in patients with positive and negative HK-2 Expression Inter-correlation of HK-2 and LDH showed no significant correlation as similar expression of HK-2 noted in both normal and abnormal LDH Level. Our findings were in discordance to the study of M.Anderson et.al in Pancreatic cancer, Alenoush et.al and Amparo Wolf et.al in glioblastoma who showed a significant

positive correlation between HK-2 and LDH.[28,29,30]

Though there was no significance of LDH activity and HK-2 expression with overall survival, majority of the patients who were dead had abnormal LDH and half of them showed positive HK-2 expression.

In conclusion, our study indicates abnormal LDH level and HK-2 expression was closely associated with patients having disease at multiple sites compared to single site, suggesting its activity to be associated with the advancement of the disease. HK-2 positivity was related with older age group strengthens the findings of increased altered metabolic activity with older age. They are also associated with BCL-2 negativity that indicates that anti-apoptotic activity of BCL-2 might be responsible for that. Though, there was no significant correlation of LDH activity and HK-2 expression with overall survival, majority of the patients who were dead had abnormal LDH and half of them showed positive HK-2 expression

Briefly, our data indicates that LDH and HK-2 can be useful parameter in defining clinical and prognostic aspects in NHL patient but needs further evaluation with larger groups of patients.

Declaration by Authors

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