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Troponin I and laboratory tests as diagnostic tools for pediatric cardiological syncope: A retrospective study in the emergency setting

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Abstract. *Background and aim:* Syncope is one of the main reasons for pediatric emergency room (PED) admission. It recognizes numerous etiopathogenetic bases, the most fearful of which is the cardiological one. Our study aims to analyze if Troponin I (TnI) and laboratory tests are helpful to identify and quickly treat cardiac causes of syncope in a pediatric emergency setting. *Methods:* We retrospectively analyzed 368 admissions to the PED of the "A. Gemelli" Hospital in Rome for syncope and presyncope, collecting medical history, physical examination, and laboratory and instrumental tests. *Results and Conclusions:* What emerged is that, in addition to a correct medical history and physical examination, there is a need to always perform a twelve-lead ECG in the presence of syncopal and presyncopal events. At the same time, Troponin I assay, and others laboratory tests seem to be not so helpful in diagnosing cardiac syncope. (www.actabiomedica.it)

Key words: pediatric cardiological syncope, troponin I, diagnostic utility, laboratory tests emergency department, pediatric syncope biomarkers, retrospective pediatric cardiology studies

Introduction

Syncope is a form of sudden and transient loss of consciousness, with or without prodrome, characterized by the inability to maintain postural tone, with spontaneous and usually complete and rapid resolution (1). It is a common event in the pediatric age; in fact, 15% of children have a syncopal episode before the eighteenth year of life and represents one of the most frequent causes of admission to the Pediatric Emergency Department (PED) (2). It is not the only etiological entity that presents these clinical characteristics; they are flanked by presyncope and pseudosyncope. Presyncope is a feeling of malaise that is reported as a sensation of impending loss of consciousness; the symptoms are usually nonspecific (dizziness, asthenia, blurred vision, nausea, difficulty maintaining an upright position) and often overlap with those associated with the prodromal phase of syncope (3). Pseudosyncope is defined as a condition that mimics syncope. It may have metabolic, neurological, and psychogenic origins (11-19% of all). This group includes dehydration, hypoglycemia, acute anemia, seizures, migraine syndromes, conversion disorders, and hyperventilation (4). The nosographic distribution of syncope is complex. However, two main groups can be identified: extracardiac syncopes due to vascular or autonomic tone-control anomalies and cardiac ones (5). Most episodes in children result from a usually benign vasovagal reaction. However, some heart conditions, potentially fatal with

elevated mortality if undiagnosed, may have a syncope as an initial manifestation. In particular, we recognize vasovagal syncope, the most common cause of syncope among children, accounting for 61-80% percent of cases presenting to the PED. Typical clinical features are a precipitating event such as standing or stress and a prodrome like dizziness, visual changes, nausea, and pallor. Breath-holding spells are part of this group (6). Cardiac syncopes, which can be structural or arrhythmic, count for 6-11,5% of all (7). Structural cardiac abnormalities include aortic stenosis, hypertrophic cardiomyopathy, coronary malformations, myocarditis, arrhythmogenic right ventricular cardiomyopathy, primary or secondary pulmonary hypertension, and Marfan syndrome with aortic dissection. Potentially fatal primary arrhythmias include polymorphic ventricular tachycardia in congenital long QT syndrome, atrial fibrillation, Wolff-Parkinson-White syndrome, and Brugada syndrome. Many children with unrepaired or repaired congenital heart disease are also at risk, especially after atrial repair of transposition of the great arteries or after Tetralogy of Fallot repair (8). Most cases of syncope may be related to an arrhythmia, which may be primary or secondary to some types of structural heart disease. Each of these conditions has an electrocardiographic equivalent or determines specifically ECG alterations that require subsequent investigations (9). Syncope of indeterminate origin represents the remaining 15-20%. Syncope is a major challenge for practicing physicians with significant resource utilization and increasing expenses because of the concern of misdiagnosing a potentially fatal condition. In an emergency setting, the goal of evaluating a child presenting with syncope is to identify life-threatening events, such as cardiac arrhythmias or structural heart diseases. These are rare but occur frequently enough to warrant diagnostic consideration (10). Moreover, blood exams, including indices of cardiac function such as Troponin I (TnI), are often performed to exclude cardiac causes of syncope. This determines a lengthening PED-stay as well as weighting on health care costs (11). Consequently, several clinical guidelines and diagnostic algorithms have been developed to optimize the diagnostic evaluation of syncope. In 2009, comprehensive Italian clinical guidelines on pediatric syncope were developed and published as a collaborative effort of several relevant societies (SIP, SIMEUP, SICP, FMSI, AIAC, SIC Sport, FIMP, GSCP, GSMESPO, SINPIA, LICE, SINC, SINP). These guidelines state that the diagnostic process for pediatric syncope may include an accurate and targeted medical history, a physical examination, including vital signs, and an ECG execution. The methods and timing of ECG and further exams depend on risk stratification derivated from medical history and physical examination (2). The goal of our study is to evaluate the usefulness of blood chemistry tests, coagulation tests, and cardiac function indices in rapidly identifying and treating potentially fatal causes of syncope in a pediatric emergency setting.

Patients and Methods

This retrospective, monocentric study enrolls a cohort of children from 1 month to 17 years old admitted for syncope to the PED of the "A. Gemelli" Hospital in Rome between 2015 and 2019.

Patients were identified from the hospital's computerized clinical record (GIPSE®) by searching for the keywords "syncope" and "presyncope" for all patients admitted to the ED. Patients were identified correctly and uniquely through the personal health code to avoid errors deriving from homonyms. The following data were collected from each medical record: age, sex, triage code, family and personal history, prodromal period, trigger events, symptoms, number of episodes, physical examination findings, ECG, blood tests, cardiologic and neurologic evaluations, electroencephalogram (EEG), radiologic tests such as computed tomography (CT) scan, magnetic resonance imaging (MRI), cardiologic investigations, final diagnosis, hospital admission, and duration of hospitalization, as applicable.

Statistical analysis

Data concerning categorical variables are expressed in numbers and percentages. Continuous variables are expressed as mean ± standard deviation. The exact Fisher-Yates test was used for non-parametric distribution. A p-value < 0.05 was required for statistical significance.

Results

During the study period in the PED of "Fondazione Policlinico Universitario Agostino Gemelli, IRCSS" 368 children diagnosed with syncope were recorded; 59.8% were female with an M: F ratio of approximately 1:1.5, with an age of 12 + 3.9 years old. All patients were evaluated at the entrance of the PED by a nurse with the assignation of a severity or triage code with a different waiting time as follows: 38.3% (142) were admitted with a green code (uncritical patient, low priority access to care), 59.2% (218) with a yellow code (moderately critical patient, quick access to treatment) and 1.9% (7) with a red code (critical patient, immediate treatment). The mean residence time in PED was 270 ± 249 minutes which corresponds to about 4.5 ± 4.1 hours, with a minimum time of 7 minutes and a maximum time of approximately 24 hours. The diagnosis and clinical categorization of patients were made by a PED physician. In particular, as shown in Figure 1, 57.6% were diagnosed with syncope, 26.1% with presyncope, and the remaining 16.3% with pseudosyncope

Patients were sub-classified into the following diagnostic categories: neurocardiogenic syncope, breath-holding spells, cardiac syncope (both structural and electrophysiological abnormalities), and pseudosyncope due to neurologic disorders including seizures, headache, and cerebrovascular disease, psychogenic problems such as hysteria/conversion, depression, panic attacks, metabolic disease (like dehydration, hypoglycemia or acute anemia) and undefined syncope. Only six patients presented a cardiac etiology (1.6%). In contrast, vasovagal and situational syncope were the most frequent (221, 60.1%), followed by indeterminate ones (78, 21.2%). The distribution by causes is summarized in Figure 2.

Most of the admissions (303, 82.3%) ended up with a home discharge, while only 34 (9.2%) with hospitalization. In Figure 3 there is the distribution by types of patient care.

The cardiological events represent the only subgroup in which the male gender prevails, with M: F = 2:1, and all of these patients are aged between 13 and 17 years old. Analyzing signs and symptoms, what emerged is that a personal or family history of heart disease, sudden death under the age of 40 years old, chest pain, and dyspnea are strictly linked to a cardiac etiology. Hot, humid, closed and crowded environments, emotional stress and pain, fever and intercurrent infectious processes, and oculo-vestibular

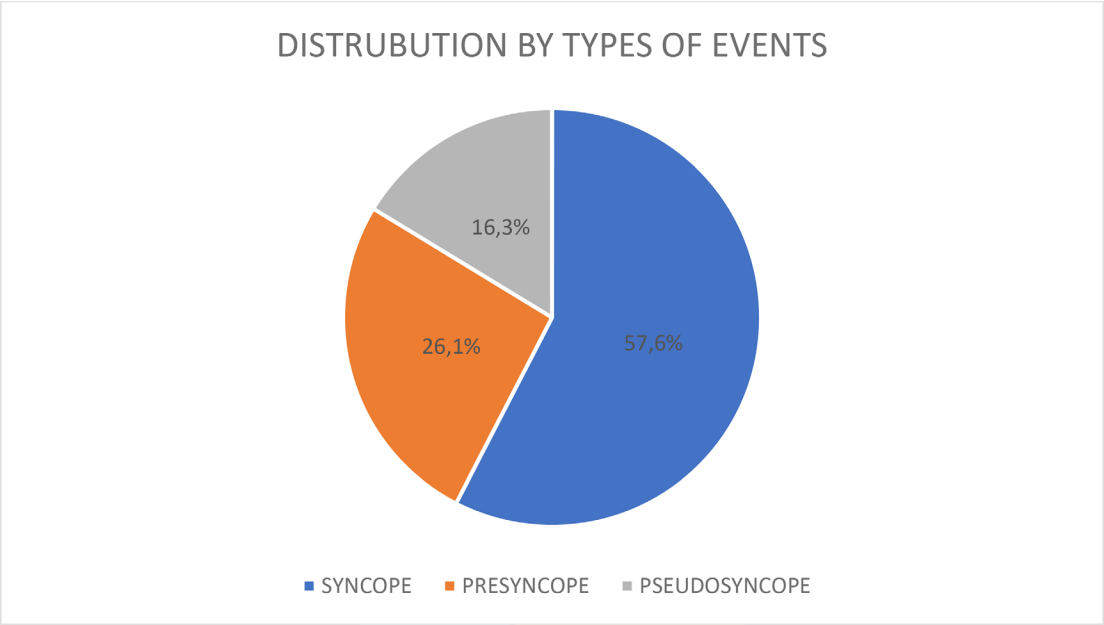

Figure 1. This shows the percentage distribution of syncope, presyncope and pseudosyncope in our sample

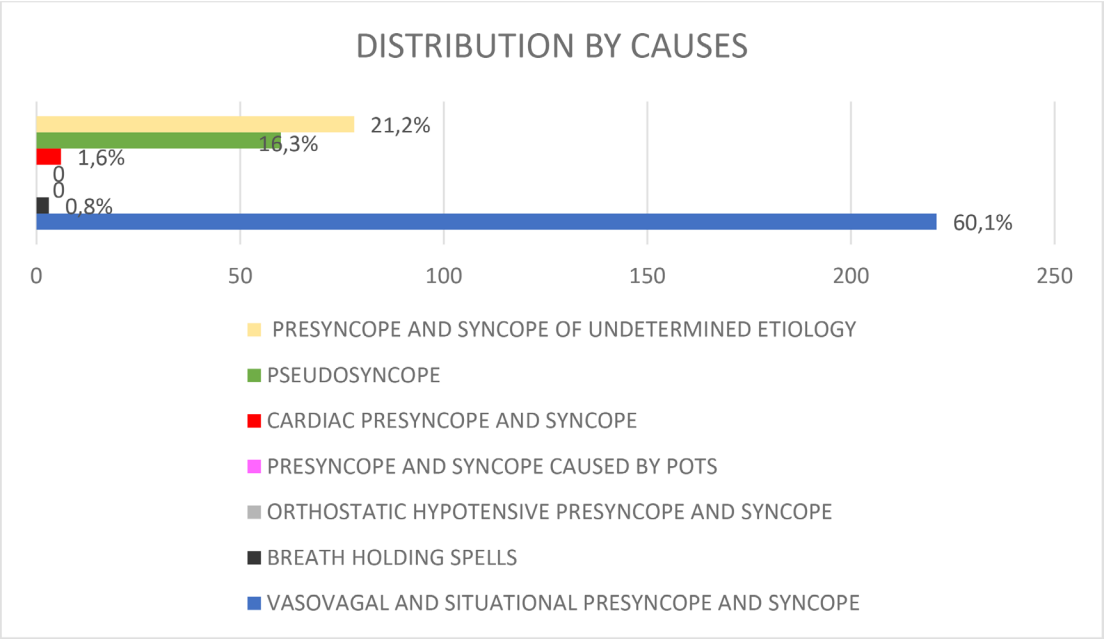

Figure 2. This shows the percentage distribution of events by causes

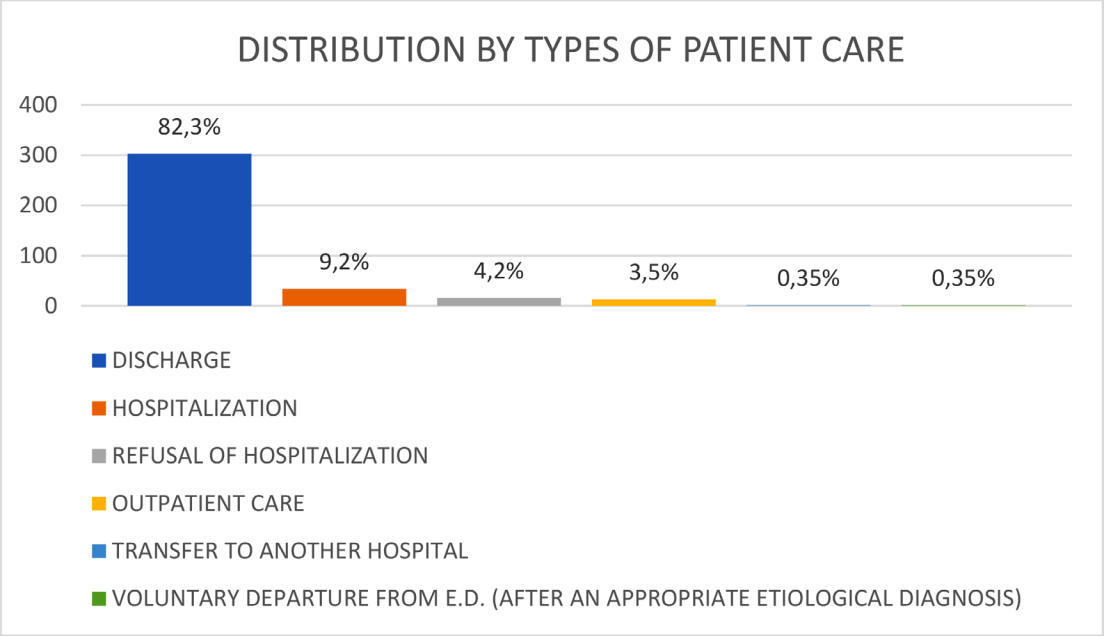

Figure 3. This shows the percentage distribution by patient discharge from Pediatric Emergency Department

symptoms (blurred vision and dizziness), are associated with vasovagal and situational syncope. Patients with prolonged loss of consciousness, seizure activity, and a postictal phase of lethargy or confusion should be considered for neurological background. Considering performed laboratory and instrumental tests, 61% of our sample underwent a blood test. Total blood count, liver and kidney function, and blood coagulation tests

always result regular, regardless of the cause of the syncope. TnI was done in 45% of cases to exclude cardiological syncope. It was found altered only in three patients, one with cardiac syncope (due to myopericarditis), the other two with vasovagal presyncope, and indeterminate syncope. As for the instrumental test, the most performed one was ECG (80% of admissions), which is the only instrumental examination indicated as mandatory by the guidelines to detect heart diseases (structural and electrical). Considering our sample's six cases with cardiological syncope, three of them showed an arrhythmic switchboard with sinus bradycardia not linked to any sporting activity. The other three patients had cardiac syncope from structural pathology (Tetralogy of Fallot subjected to cardiac surgery, myopericarditis and complex picture with pericardial effusion, pectus excavatum imprinting the right ventricle and mild mitral and tricuspid valve insufficiencies), with an ECG which documented suspected elements for heart disease. In all non-cardiac cases, the ECG does not record any anomalous pattern. EEG and neurological consultation were performed in 35 patients to identify events of neurological origin, equal to about 10% of the accesses for syncope. Only 15 were patients in which symptoms of neurological basis were highlighted during the clinical history recall. As for brain TC was done in 35 patients to exclude head trauma following a fall resulting from the syncopal event, the presence of traumatic brain injuries, or to identify conditions potentially responsible for neurological pseudosyncopes. There were no pathological findings in any of these patients. Syncope, presyncope, and pseudosyncope are common reasons for PED admission, frequently due to vasovagal cause, and ended up with a home discharge (12). Clinical manifestations of the various forms of syncope are similar, so the primary objective is to recognize severe and potentially life-threatening conditions that require immediate medical attention. Thus, only proper assessment and targeted investigations will lead to the correct diagnosis and avoid unnecessary tests and hospital admissions. Potential life-threatening events represent the minimum number of admissions, only 1.6% of our sample, but are the most dangerous ones due to the risk of a negative outcome. Hence the need to recognize the diagnostic tools that allow the doctor to identify cardiac cases. As stated by Hurst D et al and many other authors, clinical history and physical examination are the basis of every correctly carried out diagnostic process (13). In particular, the event's history is critical for developing the differential diagnosis, workup, and management plan. Likewise, thorough and detailed family history is necessary to discover the risk for sudden death, dysrhythmia, congenital heart disease, seizures, or metabolic disorders. When obtaining the history of an episode, attention should be paid to the time of last meal, activities leading up to the event, patient position at the time of symptoms, associated symptoms, and the episode's duration. During the physical examination, attention should be paid to the cardiovascular and neurologic systems, particularly chest pain and dyspnea, which must be considered red flags since they are strictly correlated to cardiac pathology. Moreover, as emerged from our case series, if these events happen in a male patient between 13 and 17 years old, the possibility of a cardiac pathological substrate increases; these are the demographic characteristics prevailing in patients with cardiac syncope. Having a look at the most performed laboratory and instrumental tests, what appeared was that TnI, which is one of the most frequently done blood tests in our sample, was dosed in 165 children and was altered in 3 cases, one of which with vasovagal presyncope, one with indeterminate syncope and one with cardiac syncope (myopericarditis); so TnI was changed only in 1 out of 6 cardiological syncopes (0.16%), with a sensitivity of 16.7% and specificity of 98.7%. TnI did not show a statistically significant correlation with cardiological events, with a p-value of 0.1058 (α <0.05). The value of TnI found in the subject with myopericarditis (5733 ng/ml at the first dose in PED and progressively increased) is significantly greater than the slight increases seen in the two non-cardiac syncopes. Furthermore, it should be considered that the patient with a high TnI also had thoracic pain whose guidelines impose troponin dosage to rule out myopericarditis. On the other hand, the correlation between the ECG findings and the diagnosis of cardiac syncope, both arrhythmical and structural, was 100%, with sensitivity and specificity respectively of 83.3% and 95.8% and a p-value less than 0.0001. A graphic explanation of these percentages is shown in Table 1.

Table 1. Troponin I and 12-lead ECG sensibility and specificity in detecting cardiac syncopes.

	Sensibility	IC_{95}	Specificity	IC_{95}
TnI	16.7%	0-45.7%	98.7%	96.7-100%
ECG	83.3%	54.3-100%	95.8%	93.8-97.8%

Other performed blood tests.

In our sample, five patients with syncope and a history of poor food intake or vomiting had low blood glucose values, detected by a glucometer. 61% of our sample underwent a laboratory blood glucose test. The correlation between hypoglycemic pseudosyncope and low blood glucose, detected by laboratory analysis, is statistically significant, with a p-value of 0.0004. However, a medical history supported by a blood glucometer test can make the diagnosis alone. Coagulation tests were required in 12% of the sample, resulting in a normal range in all cases. Considering what the guidelines state, they are not useful exams for syncopal events, except in selected cases based on a specific clinical question. Serum electrolytes (in particular sodium, potassium, and calcium) were measured in 61% of the sample. They showed slight fluctuations, which were not significant from a clinical and etiological point of view. Lactic dehydrogenase and creatine phosphokinase showed higher levels in the single myopericarditis case, not being statistically significant for predicting cardiac events (p-values respectively equal to 0.8006 and 0,5228). Plasma hemoglobin assay helped detect metabolic pseudosyncopes from acute anemia (epistaxis, hypermenorrhea). Still, it's normal in each cardiac syncope as are the total white blood cell count and platelet count. These tests are therefore not useful in detecting cardiac syncopes. The main findings in our cardiac syncope sample are resumed in Table 2.

Considering all these performed blood tests, none had a statistically significant correlation with cardiogenic syncopes. Performing blood tests significantly lengthens the permanence in the emergency room. In our study, the mean residence time in PED is 270 ± 249 minutes which corresponds to about 4.5 ± 4.1 hours, with a minimum time of 7 minutes and a maximum time of approximately 24 hours. Except for the ECG, which is mandatory, all other instrumental examinations and specialist consultations must be performed in a highly targeted manner, based on well-circumscribed clinical situations, to avoid executing unnecessary and potentially harmful tests for the patient as radiation resulting from CT scan of the skull. Our study confirms that syncope is a frequent cause of evaluation in the PED. According to the literature and most recent guidelines (SIP, SIMEUP, SICP, FMSI, AIAC, SIC Sport, FIMP, GSCP, GSMESPO, SINPIA, LICE, SINC, SINP) (2), the evaluation and management of these cases must be quick but thoughtful, in particular concerning the performance of accurate diagnostic tests, based on a detailed clinical, personal and family history. This is the first study that brings to light the scarce usefulness of laboratory tests, particularly TnI dosage, in diagnosing potential life-threatening events, particularly cardiac causes, in children admitted to the PED for syncope. Executing these tests is an economic burden for the hospital and the health system and a stress reason for the patient and the patient's family. Otherwise, it also causes a lengthening of hospitalization time in the emergency room. In conclusion, according to the main guidelines, for the diagnosis of syncopal, presyncopal, and pseudosyncopal events, the leading role is played by an accurate assessment of the clinical history, with particular attention to symptoms, trigger factors, and anamnestic data of personal and/or familiar cardiological events, and physical examination. As for laboratory and instrumental tests, executing a twelve-lead ECG is mandatory to identify cardiac syncope. In contrast, TnI assay and other blood tests are not helpful or diriment for the etiological diagnosis. Further tests should not be performed routinely without clinical signs and/or symptoms that indicate their usefulness. One of the main limitations of our study is the low turnout of pediatric patients with heart diseases, as ours is not a reference center for pediatric cardiac surgery. It would be interesting to extrapolate data from a pediatric referral cardiac center with a higher number of cardiac-based syncopes.

Table 2. Main findings in our cardiac syncope sample.

Cardiac syncopes	Gender	Age (years)	Hb (g/dL)	WBC (10^6/mmc)	Platelets (10^9/mmc)	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)	Glycemia (mg/dL)	LDH (mmol/L)	CPK (U/L)	Troponin-I (ng/L)	ECG
Sinus bradycardia	F	16	13,4	9790	166000	141	3,6	9,4	94	132	43	<0,006	Sinus rhythm. HR 47 bpm. Mild and widespread elevation of the st tract.
Sinus bradycardia	M	15	13,7	9180	270000	141	4,2	10,4	85	227	147	0,006	Sinus rhythm. HR 53 bpm. High QRS voltages.
Sinus bradycardia	M	16	16	9530	309000	140	4,3	10,4	84	183	185	<0,006	Sinus rhythm. HR 55 bpm.
Pectus excavatum with pericardial effusion and mild mitral and tricuspid insufficiency	F	17	13,1	8100	190000	139	3,7	10,3	88	143	67	<0,006	Sinus rhythm. HR bpm. Suspected anterolateral ischemia.
Myopericarditis	M	16	16,3	9250	251000	140	4,1	10,2	90	147	107	5733	Sinus rhythm. HR 64 bpm.
Surgically correct Tetralogy of Fallot	M	14	14,7	10780	201000	140	3,6	9,7	90	251	328	0,014	Sinus rhythm. HR 80 bpm. Right axial deviation, right branca block, non-specific alteration of repolarization.

Ethic Approval: Not applicable.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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