Original article

Acute coronary syndrome and cardiac biomarkers

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Abstract

Introduction: Diagnosis of acute cardiac event in the early stage of its onset is of utmost important in the treatment process whereas the development of highly sensitive and specific immunoassays for myocardial proteins such as cardiac Troponin I (cTnI) had made it possible. Given the possible complexities in establishing an early and accurate diagnosis of acute coronary syndrome (ACS), it is important for the clinician to use all available information, including the history, physical exam (PE), electrocardiogram (ECG), and cardiac biomarkers to formulate both the diagnosis of Acute coronary syndrome (ACS) and the overall assessment of patient prognosis and risk. Hence, the study was carried out to assess the clinical profiles of acute coronary syndromes and compare it with cardiac biochemical markers in Acute coronary syndrome (ACS) patients.

Methods: Hundred and eight consecutive cases of acute coronary syndrome (ACS), attending the Coronary Care Unit (CCU), of Tribhuvan University Teaching Hospital fulfilling the study criteria were taken for the present study. A record of physical findings was made and cardiovascular examination was done in each case. All the cases were scrutinized to a detail serial 12 lead electrocardiogram (ECG), serial cardiac biochemical markers- Troponin I (cTnI), Lactate dehydrogenase (LDH), aspartate transaminase (Serum Glutamate Oxaloacetate Transaminase, SGOT), and Creatine Kinase Myocardial Band (CK-MB), chest x-ray and laboratory test(e.g. Lipid profile, blood sugar), and echocardiographic study.

Results: Acute coronary syndrome was found to be more common in males (51%) than in females (49%). Ages ranged from 30 to 80 years. The common clinical presentations were chest pain (79%), palpitation (74%), sweating (71%), vomiting (45%), acute pulmonary oedema (6%), cardiac arrest (.9%) and (7%) presented with syncope. CKMB were high in about (64%), where as troponin positive cases were (60%). (89%) presented with abnormal ECG findings, STEMI was diagnosed in (33%), NSTEMI in (29%), whereas (40%) was found to have UA. Main clinical profiles were diabetes (35%), hypertension (76%), and hyperlipidemia (61%), smoking (78%), alcoholic (47%) and family history of cad (57%), over weight (25%) while obesity (36%) and abnormal WHR (69%) respectively. There was significant correlation between clinical profiles and ECG, Creatine Kinase Myocardial Band (ck_mb), troponin and types of ACS, but a slight negative correlation was detected in profiles for WHR and troponin, and fasting hyperglycemia, education, gender, diabetes, hypertension, smoking, Chest pain, heart rate, WHR, and low HDL profile with types of ACS.

Conclusion: The outcome of this study showed that the majority are male, relatively younger as compared to Western population, have smoking and hypertension followed by diabetes as the major risk factors. USA and STEMI are the dominant types of ACS and the majority of patients are likely to have hypertension, IHD and diabetes in their families. Better control of risk factors and the awareness of preventive strategies are needed.

Key words: Acute coronary syndromes, Clinical profile, electrocardiogram, cardiac biomarkers.

Introduction

Acute coronary syndrome (ACS) is a term describing any array of clinical symptoms resulting from underlying acute myocardial ischemia. ACS encompasses a wide spectrum of clinical entities, including unstable angina (UA), non-STsegment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). These conditions represent a continuum of generally increasing severity and risk, with differences in etiology, pathophysiology, presentation, and management. The clinical presentations of ischaemic heart disease include silent ischaemia, stable angina pectoris, unstable angina; myocardial infarction (MI), heart failure, and sudden death. In spite of modern treatment, the rates of death, MI, and re-admission of patients with ACS remain high[1,2,3.] The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patient is based on the electrocardiogram (ECG)[2,4]. Two categories of patients may be encountered:

(i) Patients with typical acute chest pain and persistent (>20 min) ST-segment elevation termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion.

(ii) Patients with acute chest pain but without persistent ST-segment elevation. They have rather persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalization of T-waves, or no ECG changes at presentation. The therapeutic management is guided by the final diagnosis. The management of patients with STEMI is addressed in the ESC Guidelines for management of ACS[2]. Costs of health care becomes an increasing issue in many countries. Although this should not play a role in decision making, cost consciousness is necessary today[3]. The diagnosis of NSTE-ACS is more difficult to establish than STEMI and therefore its prevalence is harder to estimate. In addition, in recent years, a new definition of MI has been introduced to take into account the use of more sensitive and more specific biomarkers of cell death[5].

American Heart Association (AHA)[6] case definition for acute myocardial infarction (AMI) requires an "adequate set" of biomarkers: 2 measurements of the same marker at least 6 hours apart. The traditional cardiac enzyme assessments for the detection of MI includes the triad of Lactate dehydrogenase (LDH), aspartate transaminase (Serum Glutamate Oxaloacetate Transaminase, SGOT), and CK-MB which is of heart origin. However the use of biochemical 'gold-standard' CK-MB levels has limited prognostic power[1]. Hence, many patients occupy CCU beds unnecessarily, and others are discharged only to return with recurrent coronary events[7]. Assessment of proteins with smaller molecular mass such as Myoglobin, Heart fatty acid binding protein (which is more cardio specific) has been developed. These appear more rapidly in the blood following the onset of necrosis and may have a specific role in the early detection of MI. However, neither of these proteins is considered as cardiac markers in clinical practice.

Identification of subjects with small areas of myocardial necrosis has become possible due to the development of specific and highly sensitive immunoassays for myocardial proteins, such as cardiac Troponins T and/or I which are components of the thin filaments of the sarcomere[8]. Studies have shown that the magnitude of Troponin elevations has correlated consistently with the risk of death and the composite risk of death or non-fatal MI, irrespective of whether the patients had ST elevation or non-ST elevation acute coronary syndromes2. Troponin I testing had better sensitivity, specificity and prognostic value than Troponin T testing. A positive Troponin I result was a strong predictor of cardiac events (death from cardiac causes or MI) in the next 30 days. The predictive value of a negative Troponin I result was also high, with a total 30-day event rate of 0.3%, regardless of the admission ECG. The new diagnostic criteria include a characteristic rise and fall in blood concentrations of cardiac Troponins in the context of spontaneous ischemic symptoms or coronary intervention[2]. Cardiac Troponin I and T are highly sensitive and highly specific and may be elevated when CK-MB concentrations are not even mildly elevated. In addition, they may predict recurrent cardiac events in patients with acute coronary syndromes. Even minor elevations of Troponin concentrations in the blood are indicative of myocyte necrosis and not due to leakage of proteins through the myocyte cell membrane[9].

The current immunoassays assays for Troponins T and I reliably detect cardiac (as distinct from skeletal muscle) forms of these proteins[2]. Furthermore, Troponins have greater sensitivity and specificity for the diagnosis of MI in acute myocardial ischemia. Given the possible complexities in establishing an early and accurate diagnosis of ACS, it is important for the clinician to use all available information, including the history, physical exam (PE), electrocardiogram (ECG), and cardiac biomarkers, to formulate both the diagnosis of UA/NSTEMI and the overall assessment of patient prognosis and risk.

The Study Objectives were to identify the clinical profile, markers of cardiac damage, cardiac biochemical markers of ACS and clinical presentation of patient with Acute coronary syndrome disease and to determine the pattern and prevalence of acute coronary syndrome disease patient

admitted in CCU. 3. To correlate the clinical profiles of patients with ACS with ECG pattern and cardiac markers.

Methods

This was a prospective cross sectional study of patients with acute coronary syndrome. Their clinical presentation was correlated with ECG and cardiac biomarkers results. This study was carried out in the in-patient Department of CCU of TUTH from 2009 to 2012. TUTH is a tertiary care hospital and referral center with all the facilities. All the patients with ACS during the study period were taken for study after fulfilling their study criteria. A total of 108 patients fulfilling the study criteria were taken for study. A correlation was done between their presenting symptoms and the cardiac biochemical markers.

Inclusion criteria

1. Presenting or admitted to hospital with symptoms suspected to represent UA or NSTEMI.
2. New onset or worsening symptoms within six hours of presentation to the ED.
3. Patient Age group from 30 Years and older
4. At least two of the three following additional criteria:
   a) Age greater than or equal to 30 years.
   b) Troponin T or I or CK-MB above the upper limit of normal for the local Institution
   c) ECG changes compatible with ischemia, i.e., ST depression at least 1mm in 2 contiguous leads or T wave inversion > 3 mm or any dynamic ST shift or transient ST elevation.
5. Written informed consent dated and signed
6. Both sexes male and female
7. Recent (≤ 7 days) ACS

Exclusion criteria

1. Age <30 years
2. Hemorrhagic stroke within the last 12 months.
3. Associated Renal disease Severe renal insufficiency (i.e., estimated creatinine clearance <20 ml/min)
4. Left Ventricular Failure, NYHA IV.
5 Persistent severe hypertension, defined as systolic blood pressure of ≥180 mm Hg or diastolic pressure of 110 mm Hg
6. Active bleeding or at high risk for bleeding (e.g., cirrhosis of the liver, any history of intracranial hemorrhage).
7. Scheduled/planned cardiac catheterization, PCI, CABG or other invasive procedure planned in the 24 weeks
8. Co-morbid condition with life expectancy less than 6 months.
11. Any contraindication to UFH or LMWH
12. Refused informed consent

Statistical Analysis

Statistical analysis was performed using the software SPSS for Windows, Version 11.5. Categorical variables were compared by chi square test and the continuous variables are presented as mean (+/- SD) and were compared by unpaired t test. Odd's ratios were calculated and presented wherever necessary. A probability value of <0.05 was considered statistically significant.

Results

Diagnosis

	Number (n=108)	Percent (%)	
STEMI	36	33.4	
NSTEMI	30	27.8	
UAP	42	38.9	
Correlation of age of patient with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
AGE			
<50	25(65.8%)	13(34.2%)	.000
>=50	14(20.0%)	56(80.0%)	
Correlation of Diabetes with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
DIABETES			
No	19(50.0%)	19(50.0%)	.027
Yes	20(28.6%)	50(71.4%)	
Correlation of clinical profile with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
Hypertension			
No	14(53.8%)	12(46.2%)	.031
Yes	25(30.5%)	57(69.5%)	
Correlation of Dyslipidemia with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
Hypercholesterolemia			
No	22(51.2%)	21(48.8%)	.008
Yes	17(26.2%)	48(73.8%)	
Correlation of smoking status with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
Smoking			
No	24(46.2%)	28(53.8%)	.036
yes	15(26.8%)	41(73.2%)	
Correlation of chest pain as a symptom with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
Chest pain			
No	12(54.5%)	10(45.5%)	.044
Yes	27(31.4%)	59(68.6%)	

Correlation of BMI with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
BMI			
No	10(23.3%)	33(76.7%)	.024
Yes	29(44.6%)	36(55.4%)	
Correlation of clinical profile with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
WHR			
Normal	17(50.0%)	17(50.0%)	.042
Abnormal	22(29.7%)	52(70.3%)	
Correlation of HBA1c with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
HBA1C			
Controlled	31(43.7%)	40(56.3%)	.024
Not controlled	8(21.6%)	29(78.4%)	
Correlation of clinical profile with CK_MB (n =108)			
Profile	CK_MB		P Value <0.05
	Normal (%)	High (%)	
Total cholesterol			
Normal	18(51.4%)	17(48.6%)	.022
High	21(28.8%)	52(71.2%)	
Correlation of clinical profile with Troponin (n =108)			
Profile	**Troponin**		**P Value <0.05**
	Normal (%)	**High (%)**	
Age			
<50	27(71.1%)	11(28.9%)	.000
>=50	17(24.3%)	53(75.7%)	
Gender			
Male	28(50.9%)	27(49.1%)	.028
Female	16(30.2%)	37(69.8%)	
Hypercholesterolemia			
No	25(58.1%)	18(41.9%)	.003
Yes	19(29.2%)	46(70.8%)	
Chest pain			
No	14(63.6%)	8(36.4%)	.014
Yes	30(34.9%)	56(65.1%)	

Correlation of clinical profile with Troponin (n =108)			
Profile	**Troponin**		**P Value <0.05**
	Negative (%)	**Positive (%)**	
Heart rate			
Normal	31(51.7%)	29(48.3%)	.010
Tachycardia	13(27.1%)	35(72.9%)	
BP			
Not Hypertensive	18(62.1%)	11(37.9%)	.006
Hypertensive	26(32.9%)	53(67.1%)	
BMI			
No	12(27.9%)	31(72.1%)	.027
Yes	32(49.2%)	33(50.8%)	
WHR			
Normal	18(52.9%)	16(47.1%)	.080
Abnormal	26(35.1%)	48(64.9%)	
Correlation of clinical profile with Troponin (n =108)			
Profile	**Troponin**		**P Value <0.05**
	Normal (%)	**High (%)**	
HBA1C			
Controlled	35(49.3%)	36(50.7%)	.012
Not controlled	9(24.3%)	28(75.7%)	
Total cholesterol			
Normal	23(65.7%)	12(34.3%)	.000
High	21(28.8%)	52(71.2%)	
Triglycerides			
Normal	17(63.0%)	10(37.0%)	.007
High	27(33.3%)	54(66.7%)	
LDL			
Normal	29(53.7%)	25(46.3%)	.006
High	15(27.8%)	39(72.2%)	

Observation

A total of 108 patients enrolled and evaluated association between glycometabolic status with CK_MB in acute coronary syndrome (ACS), Non-diabetic patients 50 %(n=19), presented with high CK_MB level where as diabetic patient 71 %(n=50) had elevated ck_mb level which was found to be statistically significant, p<.027. Patients were stratified by admission plasma glucose (<6.1 mmol/l, 6.1 – 6.9 mmol/l and ≥7.0 mmol/l) and HbA1c (≤4.5%, 4.6 – 5.4% and ≥5.5%). 78% of patients with HbA1c ≥ 5.5% had glycometabolic disturbance had strong correlation with ck_mb which was clinically and statistically significant, p<.024 compared to 56% of those with HbA1c < 5.5%. Regarding fasting hyperglycemia and pp hyperglycemia the correlation with ck_mb, it was found to be statistically significant. There was a significant (p<0.0001) correlation between CKMB and age. For example, the CKMB for subjects aged >=50 was 80%, while subjects aged <50 was 34% only. There was also significant correlations between

marital status and CKMB, p<0.007. Evaluation association between hypertensive status with CK_MB in patient with acute coronary syndrome (ACS), Non- hypertensive patients 46 %(n=12), presented with high CK_MB level where as hypertensive patient 70 % (n=57) of the total population patient studied had elevated ck_mb level which was found to be statistically significant, p<031.

Patient with clinical profile having elevated level of total cholesterol was also correlated with ck_mb and was found to be 74% (n=48), statistically significantly strong correlation p<0.008, compared to subjects with normal TC level 48 %(n=21). Similar significantly strong correlation was also seen with LDL, p<0.003. As shown in table 18, we found a strong correlation between smoking and ck mb statistically significant value, p<.036 compared to non smokers. Evaluation association between chest pain and ck_mb, patient profile with chest pain was found to have high level of ck_mb 67%, than those with no chest pain but elevated ck_mb of 45% only, p<.044 which had a significant statistical value. Regarding the correlation of BMI and WHR with level of ck_mb, again we found a strong correlation between these two parameters, p<.024 and p<.042 respectively compare to normal BMI and WHR with elevated ck_mb, which was a statistically and clinically significant correlation findings. In correlating different parameter of clinical profile with troponin in patient with ACS we found the following observation: age wise the patient presenting with troponin positive were older age >=50, than the patient who were <50 age, p<.000, and married patient were more likely to present with troponin positive, p<.008 in ACS. Significant correlation were also seen in patient with hypercholesterolemia, p<.003, gender wise, p<.028, chest pain wise, p<.014, heart rate wise, p<.010, hypertensive, p<.006, and BMI wise p<.027 than the normal subjects. Though clinically was noted to be significant in correlating WHR presented with abnormal ratio that had high level of troponin positive than with those with normal WHR, we found it not to be statistically significant in the current study, suggesting a possibility of low sample size.

Evaluation association between glycometabolic status profile and troponin in patient with acute coronary syndrome (ACS), we found that fasting hyperglycemic state did not significantly correlated with troponin than those with normal subjects presenting with positive troponin, p<.053, but a significant statistically correlation was observed with the subjects with postprandial hyperglycemia and uncontrolled HbA1C who presented with positive troponin findings, p<.028 & p<.012 respectively compared to normal subjects with positive troponin finding. Significant clinically and statistically correlation was found between high level subjects with total cholesterol p<.000, high TGL level p<.007, and high LDL level subjects p<.006, than those with normal levels but with positive troponin finding. A correlation with low HDL level though clinically relevant could not be established, the reason could be of low sample size or other factors influencing the study subjects.

Discussion

The prevalence of acute coronary syndromes is increasing. The major pathophysiologic mechanism is plaque rupture or fissuring with superimposed thrombus[10].

A positive correlation were observed with these variables of clinical profiles of patients with cardio biomarkers and types of ACS and found to be as follows: abnormal BMI was expected to have high ck_mb 36(56%) p<.024, troponin positive 33(51%) p<.027, and probability of types of ACS, UA 31(48%), STEMI 17(26%), NSTEMI 17(26%) p<.05, but a negative correlation was seen with ecg. Likewise abnormal WHR showed positive correlation with high level ck_mb 71%, p<.042, but no correlation was observed with ECG, troponin and types of ACS, than the normal subjects. This might be related, though clinically relevant, to the factors of low sample size and others parameters. Nevertheless, overweight and obesity pose a serious public health concern in Nepal in view of the rapid changes in lifestyle with processed foods increasingly replacing traditional foods. In a previous study of subjects with chest pain it was reported that Troponin was positive in 160 subjects (31.9%) and negative in 323 (64.3%) subjects[11]. They also reported higher incidence of Acute Myocardial Infarction, Acute heart failure, and death due to cardiac event in the subjects with chest pain and positive Troponin confirming that it is a powerful, independent and valuable tool for risk stratification in patients with acute chest pain. Our data indicated that, of the subjects with chest pain (108), 56 subjects (65%) were detected positive and a proportion of subjects 30(35%) were detected negative for Troponin. Accordingly; those 65% subjects with chest pain are at high risk of developing cardiac event. It is well known that increased levels of low density lipoproteins (LDL), Triglycerides (TG) and total cholesterol (TC) and decreased levels of high density lipoproteins (HDL) are also indicative of increased incidence of cardiac events and are considered a risk factor[12]. Therefore in this study the relationship between levels of lipid profile parameters and the results of Troponin test in predicting cardiac events was evaluated. The mean TC level of the subjects with positive Troponin (46, 71%) was well above the recommended desirable level (< 200 mg /dl)5 thus indicating those subjects are susceptible to develop cardiac event. The level

of total cholesterol of the subjects with negative Troponin test but with chest pain (19, 29%) was significantly lower than that of the subjects with positive Troponin above confirming the importance of maintaining total cholesterol levels below the recommended level [5,13]. Similarly the mean TG level of the subjects with positive Troponin(54, 67%) was well above the both the recommended desirable level6 (< 150 mg /dl) and the level of TG of the subjects with negative Troponin test but with chest pain (27, 33%).

The mean LDL level of the subjects with positive Troponin (39, 72%) was well above the recommended desirable level (< 130 mg /dl) [5, 12]. Further the mean LDL level of the subjects with negative Troponin test but with chest pain (15, 28%) was well below the recommended level and confirmed the importance of maintaining lower levels of LDL in preventing future cardiac event. Thus our data indicated that the subjects who developed chest pain due to cardiac event as confirmed by positive Troponin test had significantly greater levels of TC.TG, LDL when compared to those levels in subjects without cardiac event as indicated by negative Troponin test. On the other hand lower HDL level (< 40 mg/dl) is also regarded as a cardiac risk factor[13] and the mean HDL level of the subjects with positive Troponin (100, 93%) was lower than the recommended safe level. This also indicates that the development of cardiac event was associated with reduced levels of HDL than the recommended level. The total cholesterol level, TG, and LDL levels of the subjects with positive Troponin was significantly ($p < 0.000$, $p < 0.007$, $p < 0.006$) greater than subjects with negative troponin, and significant difference was observed for TC between healthy subjects and subjects with a negative Troponin test but with chest pain. Likewise significant differences were observed for TG and LDL between these groups. Similar significant correlation was observed with ck_mb and TC, p<.008, LDL p<.003, and types of ACS. Subjects with high TC value, STEMI 32(44%), followed by UA 21(29%) and NSTEMI 20(27%) showed strong association and probability than those of normal subjects. These data indicated that the chest pain due to cardiac event as determined by positive Troponin test, ck_mb is closely associated with elevated levels of TC, LDL, and TG and also with significantly reduced HDL[7].

A positive correlation was seen in our study with DM & cardio biomarkers & types of ACS. Our study shows that the number of patients with diabetes (50, 71.4%) had high elevated CKMB compared to normal subject with CKMB high, p value <.027. Patients with postprandial hyperglycemia (26, 74.3%) has probability of having positive troponin than the normal subjects in the case of ACS, p value <0.028. Similar observation were made with uncontrolled HbA1C (28, 76%) than the controlled subjects which was statistically significant, $p < 0.012$. But only small deviation was observed with fasting hyperglycemic subjects having probability of positive troponin (26, 73%) compared to normal subjects, p <0.053

Hypertension was another predictor of acute coronary syndrome in our study, particularly in men[16, 17]. The current study revealed that the subjects with high BP (57, 70%) showed probability of having elevated CKMB than the normal subjects, p value <0.031 in patients with ACS. Likewise, statistically significant correlation was made between hypertensive patients (56, 67%) of having positive troponin compared to the normal subjects with ACS, p value < 0.006. While correlating hypertension with types of ACS, the study revealed that subjects with high BP had probability of having STEMI (29,37%) more than NSTEMI (25, 32%) and UAP (25,32%) than the normal subjects, p <0.038.

In the study, current smoking status was associated with an excess risk of acute coronary syndrome events in both sexes but more in men. Tobacco consumption has increased in the last few years in Nepal[5, 7, 14,15]. The increasing rate of smoking in Nepal indicates that tobacco will make a substantial contribution to premature morbidity and mortality in the future. A strong correlation was also observed with CKMB, showing smokers (41, 73%), having a probability of elevated CKMB with ACS compared to the non-smokers, p <0.036. Whereas, correlating smoking with types of ACS and troponin did not statistically demonstrate the relation between these two variables, though, clinically relevant.

Conclusion

ACS can present a diagnostic challenge, as misdiagnosing for ACS can lead to inappropriate treatment that may cause harm, and also a failure to recognize and treat the primary diagnosis appropriately. Cardiac troponin T level rises as a result of myocyte necrosis, but does not automatically mean an ACS. Clinicians should be cautious about diagnosing ACS in patients with raised cardiac troponin T levels. Even if the ECG does not show ischemic ST-depression abnormal troponin T and I clearly establish high risk. Troponin-T is a more sensitive marker for diagnosis of ACS when compared with other cardiac biomarkers of ACS.

Since no single biomarker fulfils all of these criteria, the NACB proposes the use of two biomarkers for the diagnosis of ACS: early marker – Myoglobin and definitive marker-cardiac troponins. When cardiac troponin is not available, the next best alternative is CK-MB (measured by mass

assay). Cigarette smoking and hypercholesterolemia are the two most important, independent modifiable major risk factors for ACS at younger age. Abnormal BMI, positive family history of ischemic heart disease is also found to be one of the important risk factors in present study. WHR is an independent risk factor for ACS. Similarly, at least in men and in younger subjects, an independent association between weight and risk of ACS was noted.

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