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Association of Insulin Resistance Markers TyG Index, Lipid Ratio & Lipid Accumulation Product (LAP) with the Severity and Hospital Outcome of COVID-19 Patients

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Abstract **Original Research Article**

***Introduction*:** COVID-19 (Corona virus disease 2019) pandemic has been causing significant morbidity & mortality world-wide. Insulin resistance markers such as TyG index, lipid ratio, and LAP have been studied in relation to the severity and hospital outcome of COVID-19 patients. Early diagnosis with severity assessment and optimum supportive care is the mainstay of treatment. ***Aim of the Study*:** The aim of this study was to assess the association of insulin resistance markers TyG index, lipid ratios & lipid accumulation product (LAP) with the severity and hospital outcome of COVID-19 patients. ***Methods*:** This prospective observational study was carried out in COVID unit of BSMMU (Bangabandhu Sheikh Mujib Medical University) among hospital admitted COVID patients from March 2021 to February 2022. Total 138 COVID-19 patients were enrolled in this study. ***Result*:** Majority of patients (27.5%) was in 41-50 years age group and there was male predominance (65.9%). Majority (31.2%) of the study patients were clinically severe. There is significant correlation between disease severity and IR markers with moderate correlation with LDL/HDL and strong correlation with all other IR markers. There was significant correlation between TC/HDL and development of ARDS and & of HFNC with no other significant correlation with other outcomes. There was no significant correlation between LDL/HDL and hospital outcomes. There was significant correlation between TG/HDL and development of ARDS, also with use of rebreather and HFNC. No other significant correlation found with other outcomes. There was significant correlation between TyG index and use of rebreather & development of ARDS. No other significant correlation found with other outcomes. There was significant correlation between LAP and development of ARDS, use of rebreather & HFNC with no other significant correlation with other outcomes. ***Conclusion*:** In conclusion, this study found the insulin resistance markers TyG index. Lipid ratios and lipid accumulation product (LAP) were associated with disease severity and development of ARDS of hospitalized COVID-19 patients. Besides, TC/HDL and LAP were also associated with mortality with hospitalized COVID-19 patients.

Keywords: Insulin Resistance Markers TyG Index, Lipid Ratios, Lipid Accumulation Product (LAP), Severity, Hospital Outcome, and COVID-19 Patients.

I. INTRODUCTION

In December 2019, a cluster of patients with unknown viral pneumonia were reported in Wuhan of Wubei province in China. Then it was confirmed that the disease was caused by a novel corona virus which was named as 'Severe Acute RespiratorySyndrome-2(SARS-CoV-2)'. Since the emergence of first case, the virus rapidly spread worldwide. Up to 6th November total global confirmed cases & deaths are 48,534,508 & 1,231,017 respectively [1]. In Bangladesh, up to 6th November, 2020, total confirmed cases & deaths are 4,16,006 & 6,021 respectively [2]. The coronavirus is enveloped into ssRNA virus. The family coronaviridae is categorized into genera alpha(α), beta(β), lambda(t) & delta(δ) [3]. Alpha(α) &beta(β) genera are pathogenic

to mammals & humans [4, 5]. Like SARS-CoV & MERS-CoV, novel corona virus SARS-CoV-2 belongs to beta genus of this virus family [6]. It has 80% similarity with SARS-CoV & 50% similarity with MERS-CoV) [7]. COVID-19 pandemic outstands existing heath care facilities to support patient care all over the world. So, mild cases are taken care at home. Large number of patients & sudden deterioration of condition challenge health care management system. So, risk stratification measures are necessary for management issue [8, 9]. Early effective predictors of clinical outcomes in COVID-19 illness may help health care professionals to stratify risk of these patients. Several studies showed association of some laboratory markers with the severity & outcome of COVID-19 illness. Lymphopenia, decreased level of albumin and increased level of CRP, S. Ferritin, LDH & D-Dimer are established poor prognostic markers of the disease at early stage [6]. A part from laboratory markers, risk markers of comorbid conditions also need to addressed. Underlying risk factors for developing severe form of the COVID-19 disease & its poor outcome are patients having chronic medical illness. Insulin resistance (IR) is the known early determinant of many cardio-metabolic outcomes. Beside the gold standard marker of IR, the hyper insulin euglycemic clamp, there are many surrogate markers of IR. HOMA-IR (Homeostatic model assessment of insulin resistance) is also a well-known marker of insulin resistance. Recently the Triglyceride-glucose (TyG) index has been established a surrogate marker of insulin resistance (IR) & associated with increased risk of developing wide ranges of metabolic disorders like DM, HTN, Non-alcoholic fatty liver disease, IHD & may predict cardiovascular events [10- 12]. In addition, lipid ratios & lipid accumulation product (LAP) are also individual risk factors of insulin resistance [13]. As patients with cardiometabolic disorders are more prone to develop more severe form of COVID-19 related illness which may later lead to poorer outcome, so establishing this association of TyG index, lipid ratios & LAP with severity as well as outcome of COVID-19 is necessary for risk stratification of the disease. So far since the COVID-19 pandemic started, only few studies were done to see the correlation of disease severity of COVID-19 patient in relation metabolic marker like TyG index worldwide. Association with lipid markers of lipid ratios & LAP with this disease also yet to be addressed properly. In Bangladesh, there was no such study on these metabolic markers with COVID-19 association. So this study targets to see the association of severity & in-hospital outcome of COVID-19 patient in relation to their TyG index, lipid ratios & LAP in our country.

II. OBJECTIVES

To assess the association of insulin resistance markers TyG index, lipid ratios & lipid accumulation product (LAP) with the severity and hospital outcome of COVID-19 patients.

III. METHODOLOGY & MATERIALS

This prospective observational study was carried out in COVID unit of BSMMU (Bangabandhu Sheikh Mujib Medical University) among hospital admitted COVID patients from March 2021 to February 2022. Total 138 COVID-19 patients were enrolled in this study. All admitted patients were classified into mild, moderate, severe & critical illness as per national guideline. Baseline laboratory tests –CBC, CRP, S. ferritin, LDH, D-Dimer, SGPT, S. creatinine and fasting lipid, fasting glucose and HbA1c were done on admission. TyG index, lipid ratios and lipid accumulation product (LAP) were calculated. Radiological assessment was also done in necessary cases. Then these patients were followed up during admission period to see any disease progression and hospital outcomes. Socio- demographic data (age, sex, BMI), clinical data (symptoms & signs) & data on chronic medical illness were collected in structured pre-designed data collection sheet. Data were analyzed with the help of SPSS, Microsoft excel and Graph pad prism software.

Inclusion Criteria

- Age ≥18 with informed written consent.
- COVID-19 confirmed case by RT-PCR and or
- Radiological evidence suggestive of COVID-19.

Exclusion Criteria

- Patients with malignancy receiving chemo or radio therapy.
- Patients with poorly controlled COPD, DPLD & bronchial asthma.
- Pregnancy.
- Extreme BMI (≥40 kg/m^2).
- Patients with ESRD.
- Patients with decompensate CLD.

IV. RESULT

Total 138 patients were enrolled in this study. Table-1 describes the distribution of patients according to age group. Majority of patients (27.5%) were in 41-50 years age group. Majority of patients were male 91 (65.9%) and the rest are female 47 (34.1%), the ratio was 1.9:1. In BMI groups, 58% were normal, 32.6% were overweight and 8.7% were obese. In our study, 97.8% patients had one or more risk factors/co-morbidities. Among them 52.2% patients had DM, 44.9% had smoking history, 44.7% had HTN and 15.2% had IHD. Table-2 showing distribution of patients according to clinical severity. There were 31(22.5%) patients in mild group, 35(25.4%) in moderate, 43(31.2%) in severe and 29(21.0%) in critical group. Majority (31.2%) of the study patients were

clinically severe. Table-3 describes the frequency (median+ IQR) IR markers distribution among different severity. Among them median(IQR) of TC/HDL in mild patients 3.96(3.36-4.64), in moderate 4.79 (3.44-5.23), in severe 4.95 (4.07- 5.67), and in critical 5.77 (4.73-6.76); LDL/HDL in mild 1.93 (1.43-2.38), in moderate 2.17 (1.50-2.71), in severe 2.48 (1.97-2.79), and in critical 2.60 (2.10- 3.05); TG/HDL in mild 4.77 (3.21-6.06), in moderate 5.65 (4.23-7.00), in severe 9.33 (6.61-11.63), and in critical 9.15 (7.73-10.15); TyG index in mild 4.90 (4.69-4.98), in moderate 4.98 (4.84-5.19), in severe 5.59 (5.35-5.75), and in critical 5.53 (5.28-5.71); LAP in mild 83.37 (56.34-108.6), in moderate 91.99 (54.51-132.8), in severe 239.6 (164.4-311.6), and in critical 205.7 (157.4-328). There was overall significant difference of IR markers in different severity except LDL/HDL group ($p>0.05$). Table-4 describes correlation coefficient of disease severity and gender, age, BMI & comorbidities. The correlation coefficients of disease severity with gender (r_s)=.200, age (r_s)=.272, BMI (r_s)=.505 (r_s) & comorbidities (r_s)=.489. There was significant correlation between disease severity and age, BMI & comorbidities but not with gender. Table-5 describes correlation coefficient between disease severity and IR markers. The correlation coefficients of disease severity with TC/HDL (r_s)=.338, LDL/HDL (r_s)=.289, TG/HDL (r_s)=.444, TyG index (r_s)=.444, & LAP (r_s)=.643. There was significant correlation between disease severity and IR markers having strong correlation with LAP, moderate correlation with TG/HDL & TyG and weak correlation with TC/HDL & LDL/HDL. Table-6 describes correlation coefficient between IR markers and various hospital outcomes. The correlation coefficients between TC/HDL and hospital outcomes of use/development of rebreather (r_s)=.217, HFNC (r_s)=.282, ARDS (r_s)=.307, arrhythmia (r_s) = .201, HDU/ICU (r_s)=.200 & ventilator (r_s)=.072. There was significant correlation between TC/HDL and development of ARDS, use of rebreather & HFNC and no other significant correlation with other outcomes. The correlation coefficients between LDL/HDL and hospital outcomes of use/development of rebreather (r_s)=.211, HFNC (r_s)=.132, ARDS (r_s)=.286, arrhythmia (r_s)=.106, HDU/ICU (r_s)=.064, & ventilator (r_s)=.028. There was no significant correlation between LDL/HDL and hospital outcomes. The correlation coefficients between TG/HDL and hospital outcomes of use/development of rebreather (r_s)=.427, HFNC (r_s)=.271, ARDS (r_s)=.502, arrhythmia (r_s)=.088, HDU/ICU (r_s)=.158, & ventilator (r_s) =.041. There was significant correlation between TG/HDL and development of ARDS, also with use of rebreather and HFNC. No other significant correlation found with other outcomes. The correlation coefficients between TyG index and hospital outcomes of use/development of rebreather (r_s)=.557, HFNC (r_s)=.261, ARDS (r_s)=.626, arrhythmia (r_s)=.134, HDU/ICU (r_s)=.131 & ventilator (r_s) = .057. There was significant correlation between TyG index and use of rebreather, HFNC & development of ARDS. No other significant correlation found with other outcomes. The correlation coefficients between LAP and hospital outcomes of use/development of rebreather (r_s)=.526, HFNC (r_s)=.354, ARDS (r_s)=.654, & arrhythmia (r_s)=.112, HDU/ICU (r_s)=.203 & ventilator (r_s) =.033. There was significant correlation between LAP and development of ARDS, use of rebreather & HFNC with no other significant correlation with other outcomes.

Table I: Baseline characteristics of the study people (n=138)

Characteristics		Total	Percentage
Age (year)	21-30	8	5.8
	31-40	24	17.4
	41-50	38	27.5
	51-60	29	21
	61-70	30	21.8
	>70	9	6.5
Gender	Male	91	65.9
	Female	47	34.1
BMI	Under weight	1	0.7
	Normal	80	58
	Over weight	45	32.6
	Obese	12	8.7
Comorbidities	Smoking	62	44.9
	DM	72	52.2
	HTN	63	44.7
	Asthma	10	7.2
	COPD	8	5.8
	IHD	21	15.2
	CKD	7	5.1

	CVD	11	8
	Malignancy	1	0.7
	Others	10	7.2

Table 2: Distribution of patients according to clinical severity (n=138)

Clinical severity	n	%
Mild	31	22.5
Moderate	35	25.4
Severe	43	31.2
Critical	29	21.0

Table-3: Frequencies (Median+ IQR) & comparison IR markers with different severity (n=138)

Metabolic markers	Mild	Moderate	Severe	Critical	P-value
TC/HDL	3.96 (3.36-4.64)	4.79 (3.44-5.23)	4.95 (4.07-5.67)	5.77 (4.73-6.76)	<0.05
LDL/HDL	1.93 (1.43-2.38)	2.17 (1.50-2.71)	2.48 (1.97-2.97)	2.60 (2.10-3.05)	<0.05
TG/HDL	4.77 (3.21-6.06)	5.65 (4.23-7.00)	9.33 (6.61-11.63)	9.15 (7.73-10.17)	<0.05
TyG	4.90 (4.69-4.98)	4.98 (4.84-5.19)	5.59 (5.35-5.75)	5.53 (5.28-5.71)	<0.05
LAP	83.37 (56.34-108.6)	91.99 (54.51-132.8)	239.6 (164.4-311.6)	205.7 (157.4-328)	<0.05

Table-4: Correlation between disease severity and gender, age, BMI & comorbidities (n=138)

n=138	Pearson co-relation	Gender	Age	BMI	Comorbidities
Severity	Correlation Coefficient (r_s)	.200	.272	.505	.489
	Sig. (2-tailed)	.019	.001	.000	.000

Correlation is significant at the 0.01 level (2-tailed)

Table-5: Correlation between disease severity and IR markers (n=138)

n=138	Pearson co-relation	TC/HDL	LDL/HDL	TG/HDL	TyG	LAP
Disease severity	Correlation Coefficient (r_s)	.338	.289	.444	.444	.643
	Sig. (2-tailed)	.000	.001	.000	.000	.000

Table-6: Correlation between IR markers and hospital outcomes (n=138)

n=138	Pearson correlation	Rebreather	HFNC	ARDS	Arrythmia	HDU/ICU	Ventilator
TC/HDL	Correlation Coefficient (r_s)	.217	.282	.307	.201	.200	.072
	Sig. (2-tailed)	.010	.001	.000	.018	.019	.402
LDL/HDL	Correlation Coefficient (r_s)	.211	.132	.286	.106	.064	.028
	Sig. (2-tailed)	.013	.122	.001	.218	.453	.748
TG/HDL	Correlation Coefficient (r_s)	.427	.271	.502	.088	.158	.041
	Sig. (2-tailed)	.000	.001	.000	.303	.065	.633
TyG	Correlation Coefficient (r_s)	.557	.261	.626	.134	.131	.057
	Sig. (2-tailed)	.000	.002	.000	.117	.125	.509
LAP	Correlation Coefficient (r_s)	.536	.354	.654	.112	.203	.033
	Sig. (2-tailed)	.000	.000	.000	.192	.017	.704

V. DISCUSSION

In this study, our aim was to explore the association of insulin resistance metabolic markers TyG index, lipid ratios & LAP with COVID 19 disease severity & hospital outcomes. Basic socio-demographic characteristics were also reviewed. Total 138 COVID-19 patients were enrolled in our study. Among them, 31 patients were mild, 35 patients moderate, 43 patients severe and 29 patients were critical. In this study, 91 patients were male and 49 were female, ratio 1.9:1. There was no significant gender difference among different severity ($p>0.05$) which is similar to previous study.[14] The median+ IQR of age for all patients was 50(42-64), among them for mild patients 42(32-50), for moderate 53(47-60), for severe 47(40-62) and for critical 65(56-70). There was significant difference of median age of patients among different severity ($p<0.05$) and strong positive correlation between disease severity and age ($r_s= .272$; $p<0.001$). The median+ IQR of BMI for all patients was 24.25(22.80-26.00), among them for mild patients 22.90 (21.90-24.20), for moderate 23.50 (22.10-24.40), for severe 26.50 (25.00-28.70) and for critical 24.80 (23.20-28.10). There was significant difference of BMI of patients among different severity ($p<0.001$). In our study patients, 44.9 % were smoker or ex-smoker DM present in 52.2% cases, HTN in 44.7%, IHD in 15.2%, Asthma in 7.2%, COPD in 5.8%, Old CVD in 8% and CKD in 5.1% cases. It was observed that severity of patients was associated with presence of comorbidities which is similar to many previous studies.[15] The initial metabolic insulin resistance markers TyG index, lipid ratios & LAP were calculated. The difference of median values of IR markers between non-severe & severe group was statistically significant ($p<0.05$) except in case of LDL/HDL ($p>0.05$). In this study, correlation analysis was also done. Disease severity was not correlated with gender (r_s)= .200, & sig (2 tailed)= .019, but correlated with age, BMI & co- morbidities. The metabolic IR markers was evaluated for correlation with hospital outcome of COVID-19 patients. All measured IR markers were strongly correlated with development of ARDS (correlation significance .000). Except LDL/HDL, all others have correlation with need of rebreather and HFNC. But no IR markers had significant correlation with other hospital outcomes of development of arrhythmia, need for HDU/ICU care and ventilator support (correlation coefficient >.01). This study also focused for association of initial values of IR markers with survival outcome during hospital admission. There were initial values of TC/HDL (≥5.35), LDL/HDL (≥2.45), TG/HDL (≥7.98), TyG index (≤5.295) and LAP (≥152.63). The initial values of TC/HDL & LAP markers had worse outcomes than patients with lower level which had statistically significant($p<0.05$). In the previous study of Ren et al.[14], there was association of TyG index with disease severity & mortality. In our study, all measured metabolic markers had strong correlation with disease severity but TyG index did not show association with mortality ($p= 0.311$). But in this study, lipid based IR markers TC/HDL & LAP showed statistically significant association with mortality of hospitalized COVID-19 patients which was very new information and may the field of interest in future.

Limitations of the Study

This study was conducted in one center which is not representing our whole population parameters. In this study, COVID-19 vaccination status was not validated against disease severity. There is variable gap between symptom onset and hospital admission/consultation, which may influence parameters level and the actual picture of disease progression. Repeated measurement of laboratory parameters were not taken for analysis in this study, which might show more precise results regarding the association of these markers with COVID-19 disease progression. Disease severity may vary along course of time of study with new variant like delta and omicron. Other novel insulin resistance markers were not included in this study. So, disease severity and outcome of COVID-19 patients with measured IR marker may not fully representative.

VI. CONCLUSION AND RECOMMENDATIONS

In conclusion, this study found the insulin resistance markers TyG index. lipid ratios and lipid accumulation product (LAP) were associated with disease severity and development of ARDS of hospitalized COVID-19 patients. Besides, TC/HDL and LAP were also associated with mortality with hospitalized COVID-19 patients. Further study with larger sample size is recommended to have better understanding.

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