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Original Research Article

Assessment of Clinicopathological Parameters in Patients of Acute-On-Chronic Liver Failure with Metabolic Syndrome and Diabetes Mellitus

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Abstract

Background and Objectives: An intricate and symbiotic relationship prevails between diabetes mellitus (DM), metabolic syndrome (MetS), and hepatic afflictions such as liver cirrhosis, hepatitis, and liver carcinoma, wherein disruptions in glucose and metabolic equilibrium orchestrate a tightly interwoven linkage. However, the correlation between these conditions and the intricate domain of acute-on-chronic liver failure (ACLF) has remained insufficiently explored within recent years. Consequently, our investigation endeavors to elucidate the interplay between DM, MetS, and patients afflicted by ACLF, with the intent of harnessing this understanding as a predictive marker for disease prognosis.

Materials and Methods: A cohort encompassing 41 consecutive ACLF patients aged 18 and above was meticulously assembled, incorporating their comprehensive clinical histories, subsequently dichotomized into distinct cohorts of DM/MetS and non-DM/non-MetS categories. Anthropometric measurements and biochemical analyses was performed.

Results: DM/METS-afflicted patients exhibited conspicuous elevations across diverse demographic clinical parameters, alongside heightened levels of glycemic indices and lipid profiles. Conversely, discernible declines in protein profiles were noted, in comparison to the control counterpart of non-DM/non-MetS patients. Pertinently, concerning mortality incidence, a discernible elevation surfaced within the DM/MetS cohort, relative to the control group.

Conclusion: A heightened mortality risk and protracted hospital sojourn for ACLF patients grappling with DM/MetS was observed. The convergence of DM and MetS within the context of ACLF correlates with accentuated disease gravity, ominous prognostic trajectories, and unfavorable sequelae. Hence, the expeditious identification and adept management of these intricate comorbidities assume pivotal significance in augmenting patient outcomes.

Keywords: Diabetes Mellitus, Metabolic Syndrome, Acute-On-Chronic Liver Failure, Lipids, Glucose.

Introduction

Diabetes mellitus (DM) constitutes a chronic multifaceted ailment exerting a profound influence on the functioning of numerous vital organs, giving rise to metabolic aberrations. Notably, in 2019, the World Health Organization (WHO) documented a global toll of approximately 1.6 million fatalities attributed to DM, with projections indicating an anticipated escalation to 592 million mortalities attributed to DM by the year 2035 [1, 2]. Among the pivotal pathophysiological hallmarks characterizing DM, there exists an inadequate production of insulin, concomitant with the accumulation of unutilized glucose leading to its deposition as adipose tissue. This progression is exacerbated by sedentary lifestyles characterized by limited physical activity, which exerts deleterious repercussions on the hepatic, cardiovascular, nervous, and renal systems [3-5]. As a result, the interplay between DM and chronic liver disease (CLD) frequently materializes within the protracted course of disease advancement, yielding augmented adverse outcomes and premature mortality [6]. The liver, an indispensable organ central to the maintenance of glucose homeostasis, fulfills a critical role in both carbohydrate and lipid metabolism, while also serving as a repository for

glycogen storage [7, 8]. In recent decades, an array of scientific investigations within this realm have underscored the intricate nexus between DM and hepatic maladies such as hepatitis, liver cirrhosis, and liver cancer. These inquiries reveal that during hepatic afflictions, the equilibrium of glucose homeostasis becomes perturbed, giving rise to phenomena encompassing insulin resistance, glucose intolerance, and manifest diabetes [9].

This dysregulation engenders a diverse spectrum of hepatic disorders characterized by the progression of fibrosis, consequently compromising the attainment of Sustained Virological Response (SVR) in response to antiviral therapeutic interventions, while concurrently elevating the vulnerability to hepatocellular carcinoma (HCC) in individuals afflicted by hepatitis C virus (HCV) infection [10]. Furthermore, this perturbation is equally germane to hepatitis B virus (HBV), non-alcoholic fatty liver disease (NAFLD), and autoimmune hepatitis, collectively entrenched as potent antecedents of acute-on-chronic liver failure (ACLF). Notably, the consensus posited by the ACLF Research Consortium in 2019 elucidated a conspicuously elevated short-term mortality rate (exceeding 15% within 28 days), thereby compelling a comprehensive scrutiny of prognostic parameters [11]. However, the extant scientific literature is notably sparse in terms of comprehensive investigations into the intricate interrelation between DM and ACLF [12, 13]. Against this backdrop, our investigative endeavors are aimed at unraveling the intricate interplay linking DM and MetS with ACLF patients. This pursuit serves to explore the plausibility of utilizing DM as a potential prognostic indicator encompassing both acute and chronic manifestations of liver failure.

Material & Methods

A total of 124 individuals diagnosed with ACLF were prospectively enrolled for this study. Subsequently, for comparative analyses, patients were categorized according to the following specified inclusion and exclusion criteria:

The study's inclusion criteria encompassed individuals aged 18 years and above. Moreover, participants were categorized based on the presence or absence of diabetic metabolic syndrome. Specifically, individuals were considered eligible if their blood glucose concentration exceeded 200 mg/dL, HbA1C levels were above 6.5%, and 2-hour plasma glucose levels during an oral tolerance test surpassed 200 mg/dL. Conversely, exclusion criteria involved individuals with alcohol consumption surpassing 40 grams per week. Those who were seropositive for HIV, diagnosed with hematologic malignancies, under immunosuppressive medication, experiencing hypothyroidism, or affected by autoimmune disorders, among other specific conditions, were also excluded from the study. All instances presenting as cases of ACLF were subjected to comprehensive history-taking and a thorough array of investigations to assess their eligibility against the defined inclusion and exclusion criteria. Seropositivity for Human Immunodeficiency Virus (HIV) was evaluated for all subjects through Rapid card testing, while the confirmation of hematologic malignancies was carried out by a qualified pathologist via biopsy. Cases involving cirrhosis, hepatocellular carcinoma, and similar conditions were systematically excluded from the study. The diagnosis of diabetes mellitus and metabolic syndrome was meticulously verified to facilitate the enrollment of eligible patients into the designated case group. A cohort encompassing 41 ACLF patients aged 18 and above was meticulously assembled, incorporating their comprehensive clinical histories, subsequently dichotomized into distinct cohorts of DM/MetS and non-DM/non-MetS categories. Anthropometric measurements of all enrolled patients were meticulously recorded, accompanied by standardized clinical and biochemical assessments, adhering to prevailing clinical practice guidelines. Pertinent medical histories of patients were meticulously reviewed to ascertain the absence of diabetes and metabolic syndrome components.

Data analysis was executed utilizing SPSS 21.0 and Epi Info software. Descriptive statistics were initially computed, with quantitative data expressed as mean and standard deviation, and qualitative data presented as percentages or frequencies. For intergroup comparisons, Student's t-test and Chi-square test ($\chi 2$ test) were employed for quantitative and categorical variables, respectively. Statistical significance was defined as $p\text{-value}<0.05$.

Results

We meticulously selected a cohort of 41 ACLF patients for the purpose of this study, based on stringent adherence to our predefined inclusion and exclusion criteria. This participant pool was then classified into two experimental groups, ensuring age and sex matching: i) DM+MetS group (n=19), and ii) NonDM+NonMetS group (n=23). As indicated in Table 1, the results exhibit a comparable distribution of gender within both groups ($P>0.05$). In terms of age, it is noteworthy that DM/MS patients displayed a mean age (44.20±12.05) analogous to that of non-DM/non-MS patients (37.8±9.81) (Table 1).

Table 1: Demographic details of ACLF patients.

Parameters	DM+MetS (n=19)	NonDM+NonMetS (n=23)	P value
Age (years)	44.20±12.05	37.8±9.81	0.059
Males (n)	14	15	0.821
Females (n)	5	8	
Height (cm)	165.10±8.15	160.5±6.90	0.101
Weight (Kg)	63.75±9.85	58.20±7.75	<0.05
Waist circumference (cm)	89.20±4.80	80.10±6.15	<0.05
Hip circumference (cm)	94.10±6.05	86.20±5.90	<0.05
Mid arm circumference (cm)	24.10±2.70	22.3±1.95	<0.05

Furthermore, we conducted a thorough comparison of clinical and biochemical data. Our analysis revealed no statistically significant differences between the groups concerning the following variables: pulse, systolic blood pressure, diastolic blood pressure, hemoglobin levels (Hb%), fasting insulin levels, urea levels, creatinine levels, high-density lipoprotein (HDL) levels, conjugated bilirubin (CB) levels, total protein (TP) levels, Child-Turcotte-Pugh (CTP) scores, Model for End-Stage Liver Disease (MELD) scores, and liver size. Nevertheless, when assessing platelet counts and aspartate aminotransferase (AST) values, we observed a decline in the DM+MetS group compared to the NonDM+NonMetS group (P<0.05). Furthermore, values for fasting blood glucose (FBG), postprandial blood glucose (PPBG), hemoglobin A1C (HbA1C), and spleen size exhibited an elevation in the DM+MS group in contrast to the NonDM+NonMetS group (P<0.05). In the context of lipid profiles, we noted significantly higher values for triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and alanine aminotransferase (ALT) in DM+MetS patients compared to NonDM+NonMetS patients (P<0.01). Furthermore, we observed a decrease in albumin (ALB) levels and an increase in international normalized ratio (INR) values within the DM/MS group compared to the control group. Lastly, our analysis of death occurrence indicated a higher percentage in the DM+MetS group compared to the NonDM+NonMetS group (Table 2).

Table 2: Clinicopathological parameters of ACLF patients.

Parameters	DM+MetS (n=19)	NonDM+NonMetS (n=23)	P value
Pulse (beats/min)	96.20±8.85	94.7±11.9	0.81
Systolic BP (mmHg)	118.2±13.42	112.3±14.98	0.616
Diastolic BP (mmHg)	77.61±11.20	70.6±9.29	0.211
Hb (gm%)	11.12±1.88	10.05±3.06	0.337
Platelets (Mean±SD)	142355±48236.15	196888±91857.53	0.057
Liver Function tests			
Total Protein (gm/dL)	6.87±0.95	6.22±0.82	0.164
Albumin (g/dL)	2.67±0.48	3.02±0.52	<0.05
Total Bilirubin (mg/dL)	21.6±4.79	16.35±3.68	<0.05
Conjugated Bilirubin (mg/dL)	13.37±3.59	12.64±3.21	0.588
Child-Turcotte-Pugh Score	11.81±0.74	12.02±1.73	0.676
Model for End-Stage Liver Disease	28.86±2.46	29.5±3.68	0.729
Aspartate Aminotransferase (U/L)	135.3±75.69	374.74±52.61	<0.05
Alanine Aminotransferase (U/L)	256.8±212.14	122.05±108.32	<0.05
Liver size (cm)	12.25±3.82	10.71±2.97	0.128
Spleen size (cm)	16.24±2.96	14.07±3.34	0.079
Renal Function tests			
Serum Urea (mg/dl)	38.19±31.14	37.2±42.41	0.936
Serum Creatinine (mg/dl)	1.28±0.58	1.22±1.14	0.865
Lipid Profile			
HDL Cholesterol (mg/dL)	38.12±9.13	35.86±9.41	0.455
Triglycerides (mg/dL)	214.6±62.15	149.8±40.92	<0.05
LDL Cholesterol (mg/dL)	104.21±35.79	76.9±21.18	<0.05
VLDL Cholesterol (mg/dL)	42.15±14.93	28.6±7.98	<0.05
Blood Glucose regulation			
Fasting Blood Glucose (mg/dL)	125±36.12	80.5±9.18	<0.05
Fasting Insulin (uIU/ml)	8.22±4.79	7.87±3.72	0.735
Postprandial Blood Glucose (mg/dL)	154.52±48.31	125.7±13.82	<0.05
Hemoglobin A1c (%)	6.68±1.03	5.23±0.67	<0.05

Mortality			
International Normalized Ratio	2.87±0.52	2.36±0.48	<0.05
Death (n, %)	6 (31.58%)	4 (17.39%)	<0.05

Discussion

ACLF represents a severe clinical state characterized by the abrupt decompensation of an underlying chronic liver disease. This condition carries a substantial mortality rate and is intricately linked with the dysfunction of multiple organs. The emerging recognition of the coexistence of ACLF with comorbidities such as DM and MetS has stimulated research interest. This study was conducted to investigate and analyze the intricate relationship between ACLF patients and the presence of DM and MetS, offering valuable insights into their influence on patient outcomes.

Diabetes is frequently identified in ACLF patients experiencing the sudden deterioration of chronic liver disease. Furthermore, ACLF progression is marked by variability and complexity, often culminating in high short-term mortality, often preceded by the failure of multiple organs [14]. We observed that Hepatitis E Virus (HEV) is the likely culprit behind liver damage in both DM/MetS and non-DM/non-MetS experimental groups. This observation is consistent with the findings of the National Technical Consultation on Viral Hepatitis of New Delhi, which highlights HEV's involvement in acute hepatitis and liver failure [15]. Additionally, our analysis of lipid profiles demonstrated no significant shifts in triglyceride, LDL, HDL, or VLDL levels between the two groups. However, notable distinctions were observed in fasting blood glucose, HbA1C, and ALT values. In contrast, literature reports indicate that diabetic groups tend to exhibit higher mean AST and ALT values, with minimal changes in bilirubin, INR, triglycerides, and HDL levels [16, 17]. Similarly, reports indicate that diabetic and non-diabetic groups share comparable mean durations of acute icteric hepatitis [17]. In our investigation, the time taken for liver damage resolution was considerably lengthened in the DM+MetS group compared to the non-DM/non-MetS group.

Notably, our study unveiled no significant variance in mortality or Model for End-Stage Liver Disease (MELD) scores between cirrhotic patients with DM+MetS and those without. The dynamics of ACLF differ from those of cirrhosis in terms of rapid deterioration, heightened mortality, and potential reversibility. According to Dhiman RK, et al. [11], the average age of ACLF patients was 46±13 years. Our study's cohorts presented average ages of 42.35±11.22 years in the DM+MetS group and 35.6±9.46 years in the nonDM+nonMetS group, with 67.64% of patients being male.

Among the several etiological factors leading to acute insults that trigger ACLF, alcohol consumption (49-79%), alcoholic hepatitis (resulting in alcoholic hepatitis), hepatitis B virus (8.33%), non-alcoholic steatohepatitis (NASH) (9.16%), and cryptogenic cases (3.33%) have been highlighted [11,18-20]. There's some variance in the reported percentages regarding alcohol consumption and cryptogenic/NASH as primary causes. For most authors, alcoholic liver disease (68%) stands as the predominant cause, trailed by cryptogenic and NASH etiologies [21-24].

In terms of mortality statistics, our study found no statistically significant differences between diabetic and non-diabetic adult patients. However, a study by Lal, et al. [23] observed a 19.4% mortality rate among pediatric patients with ACLF in India. Moreover, our findings indicated increased mean values of ALT in the DM+MetS group compared to the non-DM+non-MetS group, possibly attributed to the persistent severe liver injury associated with diabetes mellitus. Collectively, the available literature and our study's findings underscore a robust association among ACLF, DM, and MetS. ACLF patients with DM or MetS tend to exhibit a poorer prognosis in comparison to those without these comorbidities. The underlying mechanisms involve a complex interplay among chronic liver disease, systemic inflammation, insulin resistance, and gut dysbiosis. Subsequent research efforts should be directed towards unraveling the intricate mechanisms that drive this association and formulating targeted therapeutic strategies to enhance outcomes for ACLF patients dealing with DM and MetS. The involvement of multidisciplinary teams encompassing hepatologists, endocrinologists, and nutritionists becomes indispensable for the comprehensive management of ACLF patients facing these interconnected challenges.

Conclusion

The simultaneous presence of DM and MetS in patients afflicted by ACLF is demonstrably linked to heightened disease severity, unfavorable prognostic trajectories, and adverse clinical outcomes. Prompt identification and adept management of these intertwined comorbidities emerge as pivotal imperatives in augmenting patient outcomes. Subsequent investigative efforts should be channeled toward crafting personalized therapeutic interventions while delving into the intricate underlying mechanisms interconnecting ACLF, DM, and MetS.

References

1. Tao Z, Shi A, Zhao J. Epidemiological perspectives of diabetes. Cell Biochem Biophys. 2015; 73:181-5.
2. World Health Organization. The top 10 causes of death [Internet]. Available from: http://www.who.int/en/news-room/factsheets/detail/the-top-10-causes-of-death.
3. Wu T, Qiao S, Shi C, Wang S, Ji G. Metabolomics window into diabetic complications. J Diabetes Investigat. 2018;9(2):244–55.
4. Eid S, Sas KM, Abcouwer SF. New insights into the mechanisms of diabetic complications: Role of lipids and lipid metabolism. Diabetologia. 2019;62(9):1539–49.
5. Yaribeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Pathophysiology of physical inactivity-dependent insulin resistance: A theoretical mechanistic review emphasizing clinical evidence. J Diabetes Res. 2021 Oct 7; 2021:7796727.
6. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. Sci Rep. 2020 Sep 8;10(1):14790.
7. Wild SH, Walker JJ, Morling JR. Cardiovascular disease, cancer, and mortality among people with type 2 diabetes and alcoholic or nonalcoholic fatty liver disease hospital admission. Diabetes Care. 2018;41(2):341–7.
8. Zhao Y, Xing H. A different perspective for management of diabetes mellitus: Controlling viral liver diseases. J Diabetes Res. 2017; 7:2017- Article ID 5625371.
9. Nishida T. Diagnosis and clinical implications of diabetes in liver cirrhosis: A focus on the oral glucose tolerance test. J Endocr Soc. 2017 May 23;1(7):886-96.
10. Hamed AE, Abas B, Shaltout I, Esmt G, Gomez R. Managing diabetes and liver disease association, guidelines (consensus) development. J Endocrinol Diabetes Obes. 2015; 3:1–19.
11. Dhiman RK, Agrawal S, Gupta T, Duseja A, Chawla Y. Chronic liver failure-sequential organ failure assessment is better than the asia-pacific association for the study of liver criteria for defining acute-on-chronic liver failure and predicting outcome. World J Gastroenterol. 2014; 20:14934–41.
12. Suman SK, Kumar A, Ghanchi CL, Ola S, Singh UN. A Comparative Study of Acute-On-Chronic Liver Failure (ACLF) Patients with Respect to Diabetes Mellitus and Metabolic Syndrome. Eur J Cardiovasc Med. [In press]. Volume:13 Issue:3; Pages 1007-1012.
13. Lai RM, Chen TB, Hu YH, Wu G, Zheng Q. Effect of type 2 diabetic mellitus in the prognosis of acute-on-chronic liver failure patients in China. World J Gastroenterol. 2021 Jun 21;27(23):3372-85.
14. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: An update. Gut. 2017; 66:541–53.
15. MoHFW-WHO-ILBS (2016) third GoI-WHO-ILBS National Technical Consultation on viral hepatitis towards a national action plan for viral hepatitis (NAP-VH). New Delhi.
16. Pradeepa R., Mohan V. The changing scenario of the diabetes epidemic: Implications for India. Indian J Med Res. 2002; 116:121–32.
17. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. Gastroenterology. 1999 Jun;116(6):1413-9.
18. Jalan R (World Gastroenterology Organization Working Party). Toward an improved definition of acute-on-chronic liver failure. Gastroenterology, 2014;147(1):4-10.
19. Moreau R (CANONIC Study Investigators of the EASL-CLIF Consortium). Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterol. 2013;144(7):1426-37, 1437.e1-9.
20. Gupta M, Dadhich S, Bhargawa N, Ranjan P, Vatsya S. Clinical profile of patients with acute-on-chronic liver failure. J Gastroenterol Liver Dis. 2016; 1(1): 1007.
21. Kumar BR, Rahul D, Prabhakar B. A study of clinical profile in patients with acute on chronic liver failure in a tertiary hospital. Asian Pac J Health Sci. 2016; 3: 47-57.
22. Shalimar, Saraswat V, Singh SP, Duseja A, Shukla A, Eapen CE, et al. Acute-on-chronic liver failure in India: The Indian National Association for Study of the Liver consortium experience. J Gastroenterol Hepatol. 2016 Oct;31(10):1742-9.
23. Lal J, Thapa BR, Rawal P, Ratho RK, Singh K. Predictors of outcome in acute-on-chronic liver failure in children. Hepatol Int. 2011 Jun;5(2):693-7.
24. Khot AA, Somani P, Rathi P, Amarapurkar A. Prognostic factors in acute-on-chronic liver failure: A prospective study from western India. Indian J Gastroenterol. 2014 Mar;33(2):119-24.