ORIGINAL ARTICLE

Quantifying the Homeostatic Model Assessment of Insulin Resistance to Predict Mortality in Multi-organ Dysfunction Syndrome

Sonu Sama[1], Gaurav Jain[2], Ravi Kant[3], Ajeet S Bhadoria[4], Manisha Naithani[5], Ajit Kumar[6]

Abstract

Background: Insulin resistance is an integral component of a multi-organ dysfunction syndrome (MODS) associated with increased mortality. We determined a cutoff value for the homeostatic model assessment of insulin resistance (HOMA-IR) during an ICU admission that could predict 28-day mortality of nondiabetic MODS patients.

Materials and methods: In this prospective, outcome assessor blinded cohort design, we evaluated 82 such patients for fasting blood glucose (FBG)/insulin levels (FIL) during an ICU admission and followed their outcome for 28 days. The primary outcome variable was the HOMA-IR score calculated from the above variables. The statistical tool included receiver operating characteristic curve, Youden index, and correlation and regression analysis.

Results: Overall, 38 patients succumbed to their illness. The optimal cutoff value for HOMA-IR was ≥1.61 (area under curve: 0.684, sensitivity: 36.8%, specificity: 95.5%). The 28-day survival was significantly lower ($p = 0.001$) at HOMA-IR threshold ≥1.61 (odds ratio: 12.25, hazard ratio: 2.98). The mean HOMA-IR among survivors vs nonsurvivors was 0.76 ± 0.61 and 1.38 ± 1.14, respectively ($p = 0.004$). Except for FIL and FBG, HOMA-IR values did not correlate with any other baseline or outcome parameters (demographics, APACHE II/sequential organ failure assessment score, vasopressor needs, or ICU/hospital stay). On comparing these parameters across the HOMA-IR threshold, only FIL and the hospital stay varied significantly. Most of the outcome parameters, however, varied significantly among nonsurvivors vs survivors.

Conclusion: The HOMA-IR is a significant predictor of mortality in MODS. Its cutoff value may assist in determining a reference range for critically ill patients. Its routine use in the light of other disease severity scores may serve in their better prognostication.

Keywords: Blood glucose monitoring, Critical illness, Diabetes mellitus, ICU mortality, Insulin resistance.

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Introduction

The multiple organ dysfunction syndrome (MODS) is a state of progressive, potentially reversible dysfunction of two or more organ systems not involved in the disorder following any acute life-threatening disruption of systemic homeostasis.[1] It is among the leading causes of mortality (50–80%) among critically ill patients.[2,3] Hyperglycemia and relative insulin resistance (IR) are the integral components of MODS. The underlying pathophysiologic mechanism includes a proinflammatory metabolic response, leading to increased secretion of pituitary hormones, amplifying the cortisol and catecholamine production. It has a counterregulatory effect on insulin function, resulting in hyperglycemia and further release of inflammatory cytokines (TNF-α and IL-1) and procoagulant factors. Thus, a vicious cycle develops, which aggravates MODS.[1,4] The IR poses a significant mortality risk even after adjustment for acute critical illness in diabetic or nondiabetic patients.[5]

IR can be quantified by both direct and indirect methods. The homeostatic model assessment of IR (HOMA-IR) is a proven and frequently used indirect marker of IR. It uses a single blood glucose value and the corresponding insulin measurement to determine the IR level.[6] Few studies have shown its prognostic value in assessing the severity of MODS and the associated mortality.[7–9] The current literature on its cutoff value that predicts mortality in critical illness is, however, sparse. We hypothesized that a cutoff value of HOMA-IR during an intensive care unit (ICU) admission could be used to predict the mortality of nondiabetic patients admitted with MODS. Our primary objective was to determine a cutoff value for HOMA-IR at ICU admission that predicts 28-day mortality in nondiabetic critically ill patients. We also analyzed its correlation with patient demographics, disease severity score, and other outcome parameters.

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Materials and Methods

After institutional ethical approval and written informed consent, we included 82 patients, aged 18–60 years, with MODS and the possibility to draw fasting blood samples (to determine blood insulin and glucose levels) within 2 hours after ICU admission, in this prospective, outcome assessor blinded, observational cohort study conducted between July 2019 and 2020 (Indian Clinical Trial Registry No: CTRI/2019/05/026174). This study was performed following the ethical principles for medical research involving human subjects as per the Helsinki Declaration 2013. MODS was defined based on history, clinical examination, and sequential organ failure assessment (SOFA) score. We excluded those with diabetes mellitus (HB1Ac ≥6.5), chronic renal failure (stage 5), malignancy, cirrhosis, pancreatitis, autoimmune disorders, currently on corticosteroid therapy, and unable to give consent. An investigator blinded to other outcome variables recorded the laboratory parameters. Another investigator who recorded patient follow-up was blinded to other aspects. Another investigator (5-year experience in critical care) blinded to outcome parameters carried out patient management.

On ICU admission, we obtained a complete medical history from patient records and through interview/s of either patients or relatives for those who are unable to converse. It followed clinical examination and drawing blood samples of patients for baseline investigations as per standard institutional protocols within 2 hours after ICU admission. The outcome parameters, including fasting insulin levels (FIL), fasting blood glucose (FBG), and glycosylated hemoglobin (HB1Ac) levels, were also measured from this sample. FIL was assessed by chemiluminescence immune assay method (ADVIA Centaur XP, Siemens, Germany), FBG was obtained by hexokinase method (Backman Coulter AU 680, USA), and HB1Ac was measured by high-performance liquid chromatography method (Toslo, Japan). The HOMA-IR value was calculated using the formulae: [HOMA-IR = glucose (mg/dL) × insulin (mU/L)/405]. All included patients received the due management and care as per the standard evidence-based protocols and were followed for 28 days after ICU admission; if discharged before that, using telephonic conversation. The recorded data included the cause for ICU admission, baseline SOFA score , type and number of organ involvement, APACHE II, FIL, FBG, and HB1Ac levels, the vasopressor requirement in ICU, mechanical ventilation days, ICU/hospital length of stay, and 28-day mortality.

The sample size was calculated using the Stata 13.0 software (Texas, USA). Taking an expected 79% sensitivity of HOMA-IR score to predict 28-day mortality in patients meeting study criteria,[10] with 10% relativity of sensitivity, 95% confidence interval (CI), and a 10% dropout rate, the sample size was calculated as 115. Only 82 patients could be enrolled in the study due to limited hospital admissions because of the COVID-19 pandemic. Ethical approval was obtained for a time-bound study taking a time limit till July 31, 2020. Statistical analysis was performed using Statistical Package for the Social Sciences version 23.0 software (SPSS, IBM Corp. Armonk, New York, USA). The results are presented as descriptive statistics and summarized as mean [standard deviation (SD)], the median [interquartile range (IQR)], or number (percentage). Data were analyzed using the receiver operating characteristic curve, Youden index, odds ratio (OR), Kaplan–Meier survival curve, and Cox regression analysis to calculate the prognostic profile of the HOMA-IR variable. The continuous variables were compared by the Mann–Whitney *U* test. The categorical variables were compared by Chi-square test/Fisher's exact test. A $p < 0.05$ was considered significant.

Results

We investigated 84 patients for eligibility, of which 82 were included in the study (Flowchart 1). The demographic profile and baseline characteristics of patients are summarized in Table 1. The majority of patients were admitted for perforation peritonitis (28%), septic shock (8%), and ARDS/pneumonitis/seizure disorder (6.1% each). The 23% of patients had comorbidities at admission, chiefly hypertension (42%) and chronic obstructive pulmonary disease

Flowchart 1: STROBE flow diagram of patients studied

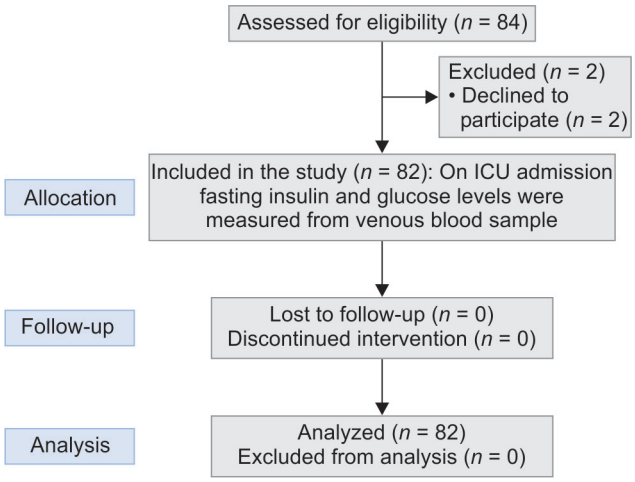


Table 1: The baseline and outcome parameters in the included patients ($n = 82$)

Sl. No.	*Parameters*		*Values*
1.	Age (years)		39.27 ± 14.44
2.	Sex (males)		46 (56.1%)
3.	Weight (kg)		58.74 ± 12.56
4.	APACHE II score		17.88 ± 6.22
5.	SOFA score		8.39 ± 3.03
6.	FIL (mU/L)		3.20 ± 3.01
7.	FBG (mg/dL)		139.39 ± 51.85
8.	HbA1c (%)		5.25 ± 0.45
9.	HOMA-IR		1.05 ± 0.94
10.	Number of organ involvement		3.35 ± 1.09
11.	Type of organ involvement	Respiratory	58 (70.7%)
		Hepatic	31 (37.8%)
		Nervous	43 (52.4%)
		Hematological	33 (40.2%)
		Hemodynamic	60 (73.2%)
		Renal	51 (62.2%)
12.	Noradrenaline requirement (mL)		255.26 ± 269.17
13.	Vasopressin requirement (mL)		26.31 ± 36.26
14.	Mechanical ventilation days		9.49 ± 9.55
15.	ICU length of stay (days)		11.59 ± 11.11
16.	Hospital length of stay (days)		18.01 ± 15.70
17.	28-day mortality		38 (46.3%)

Data presented as mean ± standard deviation, number (percentage). APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; FIL, fasting insulin levels; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance. Noradrenaline: 1 mL = 0.08 mg; Vasopressin: 1 mL = 1 unit

(31.6%). The major organ involvement included hemodynamic (73.2%), respiratory (70.7%), renal (62.2%), or nervous (52.4%) systems. The mean FIL and FBG were 3.20 ± 3.01 mU/L and 139.39 ± 51.85 mg/dL (Table 1).

In the first 28 days after ICU admission, 38 (46.34%) patients succumbed to their illness. The mean HOMA-IR was 1.05 ± 0.94, while that among survivors and nonsurvivors was 0.76 ± 0.61 and 1.38 ± 1.14, respectively. The FIL, FBG, HOMA-IR, number of involved organs, APACHE II/SOFA score, the vasopressor requirement in ICU, and hospital/ICU length of stay varied significantly among survivors vs nonsurvivors. The nonsurvivors had significantly higher hemodynamic and renal derangements (Table 2).

The optimal cutoff value of HOMA-IR that predicted 28-day mortality was calculated as ≥1.61 (sensitivity 36.8%, specificity 95.5%, Youden index 32.3) at an area under the curve (AUC) of 0.684 (CI: 0.567–0.8) and relative risk of 2.24 (CI: 1.45–3.22). A higher HOMA-IR value signified higher specificity, although it corresponded to a parallel fall in the sensitivity pattern. On comparing patients' survival at a HOMA-IR threshold of ≥1.61, we observed a significant difference among groups (p <0.001) (Table 3). The mean 28-day survival was significantly lower (p = 0.001) in patients with a HOMA-IR score of ≥1.61, evident in the Kaplan–Meier survival analysis curve (Fig. 1). The OR of 28-day mortality was 12.25 (CI: 2.56–58.54), while the associated hazard ratio (HR) was 2.98 (CI: 1.54–5.79).

We also plotted a correlation analysis between HOMA-IR and baseline parameters like age, weight, gender, APACHE II/SOFA score, and the number of involved organs, or the outcome parameters like the vasopressor requirement, mechanical ventilation days, and ICU length of stay. However, the HOMA-IR values did not correlate with any of the above parameters (Table 4). A significant positive correlation was, however, observed with FIL (r = 0.89, p <0.001) and FBG (r = 0.44, p <0.001). We observed a significant difference in only FIL (p <0.001) and hospital length of stay (p <0.039) when comparing baseline and outcome parameters at HOMA-IR cutoff of ≥1.61. We also observed lesser respiratory and higher renal involvement with a HOMA-IR score of ≥1.61, though it was statistically insignificant (Table 3).

Discussion

We measured a cutoff HOMA-IR value of ≥1.61 that predicted a significant risk of 28-day mortality of nondiabetic critically ill patients admitted to ICU with MODS. The observed diagnostic profile (sensitivity 36.8%, specificity 95.5%) highlights that only a few (2 patients) with HOMA-IR value ≥1.61 survived for 28 days after ICU admission, while many (24 patients) with above value <1.61 still succumbed to illness. The survivors with HOMA-IR score ≥1.61 had lower severity of illness at ICU admission; a higher FIL (6.6–8.7) contributed to the above HOMA-IR score in these patients. On analyzing the nonsurvivors with HOMA-IR score <1.61, we observed a higher mean APACHE II (20.42)/SOFA (10.20) score and greater organ involvement in these patients (11 had ≥4 organ dysfunction). It indicates that higher MODS severity contributed to mortality in such patients. However, a nonsignificant difference in patient demographics and APACHE II/SOFA score (at ICU admission) across HOMA-IR cutoff of 1.61 indicates that HOMA-IR is an independent predictor of mortality

Table 2: Comparison of baseline/outcome parameters among survivors vs nonsurvivors

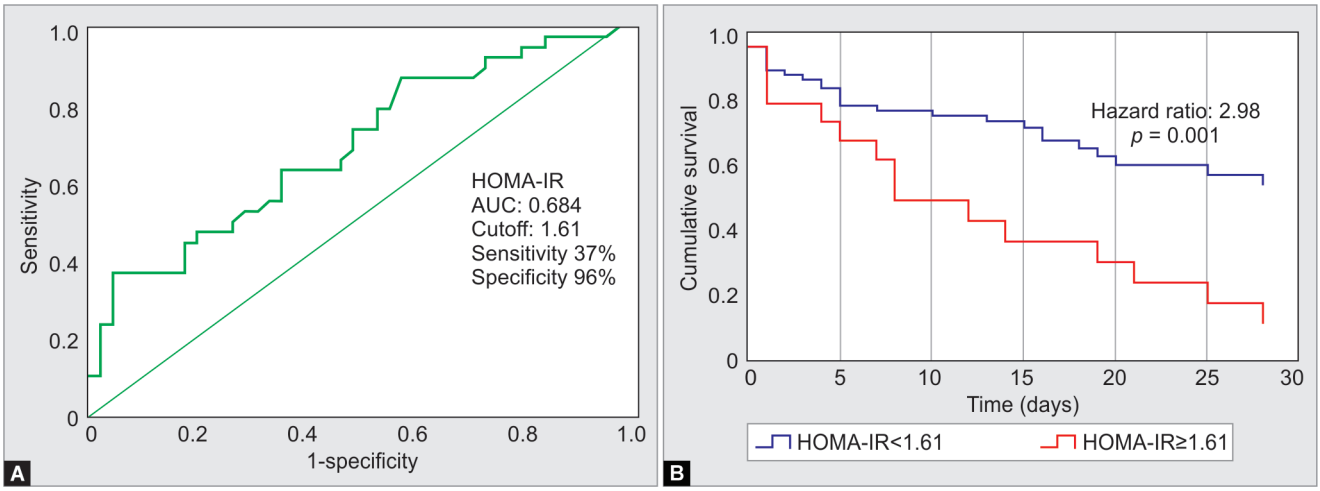
Sl. No.	*Parameters*		*Survivors (n = 44)*	*Nonsurvivors (n = 38)*	*p value*
1.	Age (years)		38.20 ± 14.80	40.50 ± 14.12	0.475
2.	Sex (males)		24 (54.5%)	22 (57.9%)	0.761
3.	Weight (kg)		58.09 ± 12.62	59.50 ± 12.63	0.616
4.	APACHE II score		16.23 ± 5.54	19.79 ± 6.48	0.009
5.	SOFA score		7.16 ± 2.13	9.82 ± 3.30	<0.001
6.	FIL (mU/L)		2.48 ± 1.88	4.03 ± 3.80	0.027
7.	FBG (mg/dL)		126.68 ± 38.26	154.11 ± 61.39	0.020
8.	HOMA-IR		0.76 ± 0.61	1.38 ± 1.14	0.004
9.	HbA1c (%)		5.23 ± 0.47	5.25 ± 0.41	0.831
10.	No. of organ involvement		3.02 ± 0.97	3.71 ± 1.13	0.005
11.	Type of organ involvement	Respiratory	31 (70.5%)	27 (71.1%)	0.953
		Hepatic	15 (34.1%)	16 (42.1%)	0.455
		Nervous	20 (45.5%)	23 (60.5%)	0.173
		Hematological	17 (38.6%)	16 (42.1%)	0.749
		Hemodynamic	28 (63.6%)	32 (84.2%)	0.036
		Renal	23 (52.3%)	28 (73.7%)	0.046
12.	Noradrenaline requirement (mL)		137.63 ± 220.51	391.47 ± 258.05	<0.001
13.	Vasopressin requirement (mL)		7.52 ± 19.01	48.07 ± 39.40	<0.001
14.	Mechanical ventilation days		10.82 ± 10.97	7.95 ± 7.45	0.165
15.	ICU length of stay (days)		14.48 ± 12.82	8.24 ± 7.60	0.008
16.	Hospital length of stay (days)		24.91 ± 17.25	10.03 ± 8.47	<0.001

Data presented as mean ± standard deviation, number (percentage). APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; FIL, fasting insulin levels; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance. Noradrenaline; 1 mL = 0.08 mg; Vasopressin: 1 mL = 1 unit. A p <0.05 is considered significant

Table 3: Comparison of baseline/outcome parameters at threshold value of HOMA-IR

Sl. No.	*Parameters*		*HOMA-IR <1.61 (n = 66)*	*HOMA-IR ≥ 1.61 (n = 16)*	*p value*
1.	Age (years)		39.45 ± 14.43	38.50 ± 14.91	0.819
2.	Sex (males)		37 (56.0%)	9 (56.2%)	0.836
3.	Weight (kg)		57.76 ± 12.14	62.81 ± 13.84	0.194
4.	APACHE II		17.79 ± 6.39	18.25 ± 5.58	0.792
5.	SOFA score		8.3 ± 3.06	8.75 ± 2.95	0.595
6.	FIL (mU/L)		2.17 ± 1.36	7.42 ± 4.16	<0.001
7.	FBG (mg/dL)		134.33 ± 50.60	160.25 ± 53.29	0.092
8.	HbA1c (%)		5.235.23 ± 0.47	5.295.23 ± 0.33	0.579
9.	No. of organ involvement		3.33 ± 1.12	3.38 ± 1.02	0.887
10.	Type of organ involvement	Respiratory	49 (74.2%)	9 (56.2%)	0.156
		Hepatic	25 (37.8%)	6 (37.5%)	0.978
		Nervous	35 (53%)	8 (50%)	0.828
		Hematological	26 (39%)	7 (43%)	0.750
		Hemodynamic	48 (72%)	12 (75%)	0.854
		Renal	27 (60%)	12 (75%)	0.239
11.	Noradrenaline requirement (mL)		223.13 ± 245.09	387.81 ± 328.13	0.075
12.	Vasopressin requirement (mL)		22.66 ± 33.47	41.36 ± 44.103	0.128
13.	Mechanical ventilation days		9.56 ± 9.84	9.19 ± 8.53	0.880
14.	ICU length of stay (days)		11.98 ± 11.53	9.94 ± 9.27	0.458
15.	Hospital length of stay (days)		19.39 ± 16.50	12.31 ± 10.40	0.039
16.	28-day mortality		24 (36.4%)	14 (87.5%)	<0.001

Data presented as mean ± standard deviation, number (percentage). APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; FIL, fasting insulin levels; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance. Noradrenaline: 1 mL = 0.08 mg; Vasopressin: 1 mL = 1 unit. A p <0.05 is considered significant



Figs 1A and B: Receiver operating characteristic curve (A) and Kaplan-Meier survival analysis (B) showing a prognostic profile of HOMA-IR in predicting 28-day mortality

in MODS. It further indicates that IR plays a vital role in MODS pathogenesis.

Ideally, the HOMA-IR value for a nondiabetic healthy individual should be around 1, but it gets affected by sociodemographic characteristics, ethnicity, and pathophysiological factors.[11,12] Several studies have shown a cutoff HOMA-IR value of 1.5–3 that is associated with the risk of metabolic syndrome or cardiovascular events in the adult population.[12,13] Though the current data are limited to mean HOMA-IR scores in critically ill patients, it signifies an association between the higher HOMA-IR values and the acute kidney injury/mortality.[9,14] Khan S et al. measured a mean HOMA-IR score of 2.41 in euglycemic septic shock patients while measuring a value of 5.20 for hyperglycemic patients.[9] In MODS patients, Das et al. obtained a mean HOMA-IR value of 5.14 vs 7.16 while Gupta et al. obtained a mean HOMA-IR value of 0.9 vs 2.24 among survivors vs nonsurvivors, respectively.[7,8] We observed a mean HOMA-IR score of 1.38 vs 0.76 among nonsurvivors vs survivors. Though all the above studies were conducted on the Indian population, inherent

Table 4: Correlation analysis between HOMA-IR and the baseline/outcome parameters in the included patients

Sl. No.	*Parameters*	*Correlation coefficient (r)*	*p value*
1.	Age (years)	0.05	0.664
2.	Weight (kg)	0.07	0.545
3.	APACHE II	0.11	0.314
4.	SOFA score	0.09	0.433
5.	FIL (mU/L)	0.89	<0.001
6.	FBG (mg/dL)	0.44	<0.001
7.	Number of organ involvement	0.04	0.682
8.	Noradrenaline requirement (mL)	0.12	0.341
9.	Vasopressin requirement (mL)	0.12	0.482
10.	Mechanical ventilation days	0	0.974
11.	ICU length of stay (days)	−0.06	0.606
12.	Hospital length of stay (days)	−0.17	0.135

APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; FIL, fasting insulin levels; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance. A p <0.05 is considered significant

differences in unaccounted factors including primary diagnosis, comorbidities, and demographic characteristics could account for the difference in HOMA-IR values. A sample size lesser than the targeted number may have also affected the results. Bonora et al. observed that the risk of cardiovascular disease increased by 1.31 (OR) per unit increase in HOMA-IR score in type 2 diabetics.[15] We observed an OR value of 12.25 for 28-day mortality in MODS; it indicates that the degree of IR has a far more significant impact on the outcome of such ICU patients.

In the Cox model, we calculated an HR of 2.98 for 28-day mortality at a HOMA-IR threshold of ≥1.61. It correlates with the observations by Van Vught et al., who calculated an HR of 1.66 for 30-day mortality in critically ill patients admitted with severe hyperglycemia.[16] Nakamura et al. also calculated a 1st, 2nd, 3rd, and 4th tertile HR of ≤0.66, 1.07, 1.36, and 2.50 for HOMA-IR to assess the associated risk of cardiovascular events in nondiabetic individuals.[17] Our observations though indicate a higher risk of mortality with IR in MODS. The underlying pathophysiologic cascade in such patients stimulates insulin secretion from the pancreatic beta cells but deters the insulin responsiveness in the target organ systems. It induces a hyperinsulinemic–hyperglycemic state along with IR.[8] However, continuous stimulation, especially in moribund patients, eventually leads to beta-cell failure, and thus low insulin levels can be observed in severely ill patients. Das et al. observed a higher FBG and low FIL in patients who died of MODS, though it attained a nonsignificant difference.[8] We observed a significantly higher value of both FBG and FIL among nonsurvivors, which signifies their correlation with mortality. The inclusion of patients with lesser organ involvement (only 16% with >4 organs involved as opposed to 43% in the study by Das et al.) or presentation at an early stage of their illness could contribute to the above results. We also plotted a correlation analysis between the HOMA-IR values and the baseline/outcome parameters at ICU admission but observed a significant association with that for FIL and FBG only. On comparing these parameters at a HOMA-IR threshold of ≥1.61, patients with higher HOMA-IR (≥1.61) had a significantly shorter hospital length of stay. It is attributed to early mortality in such patients.

This study has a few limitations. In the restricted time frame for the completion of the study, we had to limit the sample size due to the ongoing COVID-19 pandemic. Though we could achieve a significant AUC for HOMA-IR values, a limited sample size could have been reflected as low HOMA-IR cutoff sensitivity (36.8%) and a corresponding Youden index of 32.3. It could also have contributed to the nonsignificant difference in some of the outcome variables. This study, however, generates sufficient data to plan suitably powered future trials. Secondly, there is a lack of consensus on an ideal laboratory assay for estimating FIL. Although HOMA-IR is affected by FIL, we chose it in view of lower cost, convenience in obtaining results, and considering a good reported correlation with the hyperinsulinemic–euglycemic clamp method, a gold standard for evaluating the IR.

In conclusion, the optimal HOMA-IR value associated with the mortality of MODS patients was ≥1.61 for the overall study sample. It may serve in determining a new reference range for ICU patients. Looking at HOMA-IR values in combination with other ICU scoring systems may serve in better prognostication of critically ill patients.

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