Acute Illness with Extreme Hyperglycemia

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Objectives:

To evaluate correlations between plasma glucose to glycated hemoglobin ratio (GAR) and clinical outcomes during acute illness.

Methods:

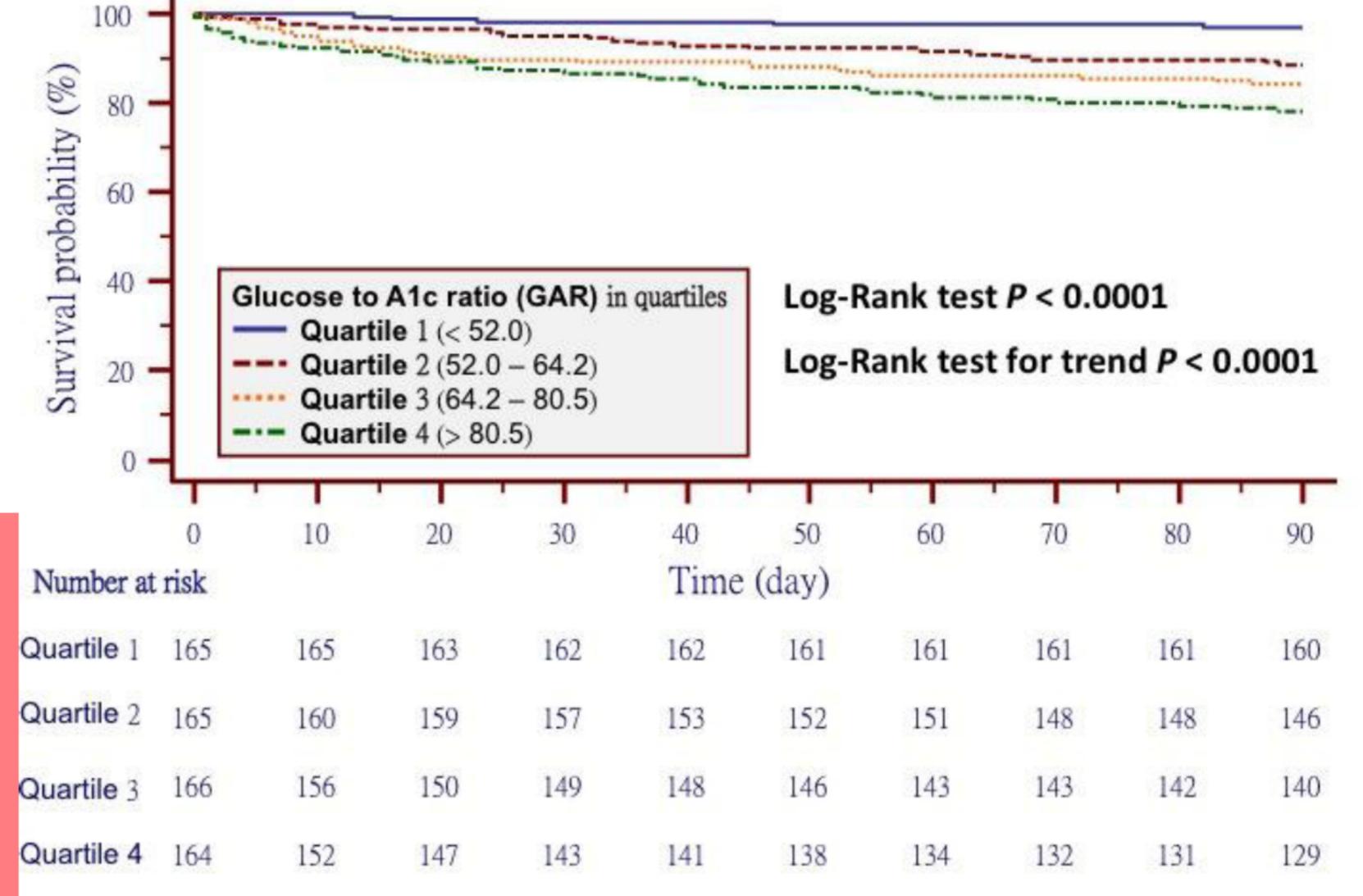
This is a retrospective, observational cohort study. We enrolled six hundred and sixty-one patients who visited the emergency department of our hospital between July 1, 2008 and September 30, 2010 with a plasma glucose concentration >500 ml/dl. Systolic blood pressure, heart rate, plasma glucose, white blood cell, neutrophil, hematocrit, blood urea nitrogen, serum creatinine, liver function, and plasma glucose concentration were recorded at the initial presentation to the emergency department. Data on glycated hemoglobin over the preceding 6 months were reviewed from our hospital database. Glucose to HbA1C ratio (GAR) was calculated as the plasma glucose concentration divided by glycated hemoglobin.

Factors associated with 90-day all-cause mortality by Cox regression analysis

90-day survival probability stratified by GAR quartile. There was a significant trend toward

decreasing survival from Q1 to Q4 (log-rank test for trend p<0.0001).

	Crude HR (95% CI) per 1-SD Increase		Adjusted HR (95% CI) per 1-SD Increase	
	HR (95% CI)	p value	HR (95% CI)	p value
GAR	1.41 (1.22-1.63)	< 0.001	1.29 (1.05-1.57)	0.013
Age	1.55 (1.20-2.01)	0.001	1.63 (1.20-2.22)	0.002
Plasma glucose	0.89 (0.70-1.13)	0.328	_	-
SBP	0.45 (0.28-0.71)	0.001	0.70 (0.44-1.12)	0.132
Serum creatinine	1.19 (1.05-1.35)	0.005	1.15 (0.93-1.43)	0.206
Hct	0.63 (0.52-0.77)	< 0.001	0.71 (0.56-0.91)	0.006
Platelet	0.76 (0.60-0.97)	0.030	0.87 (0.69-1.10)	0.251
ANC	1.29 (1.09-1.53)	0.003	1.05 (0.84-1.30)	0.678
CRP	1.41 (1.20-1.65)	< 0.001	1.31 (1.06-1.62)	0.013



Results:

The GAR of those who died was significantly higher than in the survivors (81.0 ± 25.9 vs. 67.6 ± 25.0, p<0.001). There was a trend toward a higher 90-day mortality rate in the patients with a higher GAR (log-rank test for trend p<0.0001). In multivariat Cox regression analysis, GAR was significantly related to 90-day mortality (hazard ratio [HR] 1.41, 95% confidence interval [CI]: 1.22-1.63, p<0.001), but not plasma glucose (HR: 0.89, 95% CI: 0.70-1.13, p=0.328). The rates of intensive care unit admission and mechanical ventilator use were also higher in those with a higher GAR.

Conclusions:

GAR independently predicted 90-day mortality, intensive care unit admission, and use of mechanical ventilation. It was a better predictor of patient outcomes than plasma glucose in patients with extremely high glucose levels.

[1]Vanhorebeek I, Langouche L. Molecular mechanisms behind clinical benefits of intensive insulin therapy during critical illness: glucose versus insulin. Best Pract Res Clin Anaesthesiol. 2009; 23: 449-459 [2]Boonen E, Van den Berghe G. Endocrine responses to critical illness: novel insights and therapeutic implications. J Clin Endocrinol Metab. 2014; 99: 1569-1582

[3]Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009; 373: 1798-1807 [4]Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma. 2005; 59: 80-83

[5]Siegelaar SE, Hermanides J, Oudemans-van Straaten HM, et al. Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. Crit Care. 2010; 14: R224

[6]Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma. 2004; 56: 1058-1062

[7]Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009; 37: 3001-3009

[8] Christiansen C, Toft P, Jorgensen HS, Andersen SK, Tonnesen E. Hyperglycaemia and mortality in critically ill patients. A prospective study. Intensive Care Med. 2004; 30: 1685-1688 [9]Chi A, Lissauer ME, Kirchoffner J, Scalea TM, Johnson SB. Effect of glycemic state on hospital mortality in critically ill surgical patients. Am Surg. 2011; 77: 1483-1489

[10]Krinsley JS, Meyfroidt G, van den Berghe G, Egi M, Bellomo R. The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. Curr Opin Clin Nutr Metab Care. 2012; **15**: 151-160

[11]Smith FG, Sheehy AM, Vincent JL, Coursin DB. Critical illness-induced dysglycaemia: diabetes and beyond. Crit Care. 2010; 14: 327

[12]Rady MY, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. Mayo Clin Proc.

2005; **80**: 1558-1567 [13]Krinsley JS. Glycemic control in the critically ill - 3 domains and diabetic status means one size does not fit all! Crit Care. 2013; 17: 131

[14]Guo YW, Wu TE, Chen HS. Prognostic factors of mortality among patients with severe hyperglycemia. Am J Manag Care. 2015; 21: e9-e22 [15]Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med. 2012; 40: 3180-3188

[16]Bagshaw SM, Egi M, George C, Bellomo R, Australia New Zealand Intensive Care Society Database Management C. Early blood glucose control and mortality in critically ill patients in Australia. Crit Care Med. 2009; **37**: 463-470

[17]Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med. 2005; 33: 2772-2777 [18]Egi M, Bellomo R, Stachowski E, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med. 2011; 39: 105-111

[19]Zhang ZL, Che XM, Bai ZH, Bu WJ, Bai L, Pei HH. Prognostic and assessment value of hyperglycemia and glycosylated hemoglobin in critical patients. Genet Mol Res. 2014; 13: 7006-7012

[20] Stegenga ME, Vincent JL, Vail GM, et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. Crit Care Med. 2010; 38: 539-545 [21] Van Cromphaut SJ. Hyperglycaemia as part of the stress response: the underlying mechanisms. Best Pract Res Clin Anaesthesiol. 2009; 23: 375-386

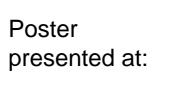
[22]Roberts GW, Quinn SJ, Valentine N, et al. Relative Hyperglycemia, a Marker of Critical Illness: Introducing the Stress Hyperglycemia Ratio. J Clin Endocrinol Metab. 2015; 100: 4490-4497

[23]Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008; 31: 1473-1478 [24]Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and

NAD(P)H-oxidase activation. Diabetes. 2003; 52: 2795-2804 [25]Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295: 1681-1687 [26]Risso A, Mercuri F, Quagliaro L, Damante G, Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. Am J Physiol Endocrinol Metab. 2001; 281: E924-930

[27]Cohen G, Riahi Y, Alpert E, Gruzman A, Sasson S. The roles of hyperglycaemia and oxidative stress in the rise and collapse of the natural protective mechanism against vascular endothelial cell dysfunction in diabetes. Arch Physiol Biochem. 2007; 113: 259-267 [28]Oleszczak B, Szablewski L, Pliszka M. The effect of hyperglycemia and hypoglycemia on glucose transport and expression of glucose transporters in human lymphocytes B and T: an in vitro study. Diabetes Res









Clin Pract. 2012; **96**: 170-178