



Original Research Article

An exploration of glycemic gap as a biomarker to predict intensity and consequence of pulmonary embolism in diabetic patients

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ABSTRACT

Background : Pulmonary embolism is a substantial disease with high rate of both morbidity and mortality, which becomes more prevalent in documented diabetic patients.

The aim of the present study was to evaluate the contribution of glycemic gap as a biomarker towards defining the intensity and consequence of pulmonary embolism in diabetic patients.

Materials and Methods: Diabetic patients who were admitted to Khaja Banda Nawaz Institute of Medical Sciences with a confirmed diagnosis of pulmonary embolism, during the period between January 2019 and September 2020 were enlisted for the present study. Patients selected for the study were in the age group of ≥ 18 years and they were from either gender.

Results: The present study selected 162 diabetic patients (among them 80 were females and 82 were males), with mean age of 48.6 ± 6.6 years. Out of 162 patients, 136 (84%) were survivors and 26 (16.0%) were non-survivors. Among survivors, 13 (8%) patients showed clinical deterioration with time and 21 (12.8%) patients needed ICU admission. Non-survivors had advanced age group (53.3 ± 3.4 vs. 49.2 ± 3.2 , $p=0.002$), higher PESI (102 ± 21.7 vs. 74.6 ± 14.3 , $p<0.001$) and prolonged hospital stay (4.9 ± 0.29 days vs. 4.1 ± 0.23 days, $p<0.001$). There was a highly significant difference regarding the glycemic gap between non-survivors and survivors (37.3 ± 9.3 vs. 83.1 ± 11.6 , $p<0.001$), patients with and without clinical deterioration (104.02 ± 12.3 vs. 47.2 ± 12.3 , $p<0.001$), and patients who were and were not in-need of ICU admission (43.1 ± 14.8 vs. 106.2 ± 23.7 , $p<0.001$).

Conclusion: Results of the present study proves that uplifted level of glycemic gap between serum glucose levels upon admission and the HbA1c-derived average glucose was showing strong correlation to the increase in rigourness of disease along with rate of mortality in diabetic patients with pulmonary embolism. Therefore, we proposed to use glycemic gap as a biomarker in predicting the severity and prognosis of pulmonary embolism.

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1. Introduction

Diabetes mellitus is a reported risk factor for pulmonary embolism, and a meta-analysis estimated a 1.4-fold increased risk for persons with diabetes.¹ However, analyses of data from the Nurses' Health Study and from the Heart and Estrogen/progestin Replacement Study (HERS) failed to find an association between diabetes and Pulmonary embolism.² This could be explained by the fact

that persons with diabetes are frequently hospitalized for major surgery or acute medical illness, or confined to a nursing home or chronic rehabilitation facility, all of which are major risk factors for incident pulmonary embolism.³ Consequently, we hypothesized that diabetes is not an independent risk factor for incident pulmonary embolism after controlling for previously identified pulmonary embolism risk factors.

We performed a population-based case-control study to test diabetes mellitus for an association with incident

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pulmonary embolism, both alone and after controlling for other pulmonary embolism risk factors. We also tested the association of diabetes with incident idiopathic pulmonary embolism. We wished to test the entire spectrum of diabetes mellitus occurring in the community for an association with pulmonary embolism. Therefore, for the purposes of this study, we used a very broad definition of diabetes (i.e., any mention of diabetes within the complete medical record prior to the incident pulmonary embolism), and a very strict but possibly less sensitive definition of diabetes (i.e., evidence of any ambulatory [outpatient] fasting blood glucose 140 mg/dL or antidiabetic drug therapy before the incident pulmonary embolism).⁴

Diabetes may be complicated by microvascular occlusive disease, manifest as diabetic retinopathy, nephropathy, or neuropathy. The same process that causes such arterial vascular disease among persons with diabetes has been suggested to cause pulmonary embolism.⁵ To the best of our knowledge no prospective study has been conducted till now to analyse the role of glycaemic gap in diabetic patients with pulmonary embolism, therefore, the present study was designed specifically to analyse the role of glycaemic gap as a biomarker in defining the intensity and consequences of pulmonary embolism in diabetic patients.

2. Materials and Methods

The prospective study included the diabetic patients who got admitted from January 2019 till September 2020 in Khaja Banda Nawaz Institute of Medical Sciences with a confirmed diagnosis of pulmonary embolism for the treatment purpose.

2.1. Inclusion criteria

All the enlisted subjects were of either gender in the age group of 18 or more than that having confirmed diagnosis of pulmonary embolism.

2.2. Exclusion criteria

1. Patients with diabetic ketoacidosis or hyperosmolar hyperglycemic state during admission were excluded.
2. If any patient is having history of taking therapeutic anticoagulant for more than 24 hours.
3. Diabetic patient with HbA1c level equal to or greater than 6.5% were excluded.
4. Patients on steroid therapy.

2.3. Evaluation of blood glucose level, HbA1c, and glycaemic gap

As soon as patient got admitted, the blood glucose level was measured with standard methods. To measure HbA1c level, a blood analyzer was used. For the briefing of previous 3 months, the customary equation $AG = 28.7A - HbA1c - 46.7$

was followed, where HbA1c levels got converted to get the long-term average glucose levels (eAG).⁶ Follow-up of enlisted patients were done till the completion of present study and the results were prepared in tabulated form.

2.4. Statistical analysis

Categorical variables of the study were defined as number/percentage, whereas continuous variables defined as the mean (SD). As per standard methods, two groups were compared using

Independent student's t-test, and to compare more than two groups ANOVA test was followed. To compare % of categorical variables Pearson's χ^2 -test and to predict relationship between parametric data Pearson's correlation coefficient was applied, where (+) sign indicates direct and (–) sign indicates inverse correlation. Binary logistic regression was done to estimate risk estimation. Statistically significance was considered if p value less than 0.05. All statistical analyses were performed using SPSS 22.0.

3. Results

Present study enlisted total 162 diabetic patients; among them 80 were females and 82 were males, with mean age of 48.6 ± 6.6 years. Out of 162 patients, 136(84%) were survivors and 26 (16.0%) were non-survivors. Considering habits, 79(48.7%) patients were smokers among survivors and 12(46.1%) among non-survivors. Clinical outcome in the studied diabetic patients with pulmonary embolism depicts 13 (8%) patients evolved with clinical deterioration and 21(12.8) patients needed ICU admission whereas remaining 141 patients (86.5%) not needed ICU at all. Table 1 depicts statistically significant difference ($p < 0.001$) between survivors and non-survivors as more aged patient, longer length of hospital stay (LOS) and higher pulmonary embolism severity index (PESI) was seen among non-survivors. On the contrary, there was no significant difference was seen between both the groups related to gender distribution, body-mass index (BMI), habits (smoking), and presence of comorbidities.

Table 2 Shows highly significant difference considering readings of glycaemic gap between non-survivors and survivors, patients with and without clinical deterioration, and patients who were and were not in-need of ICU admission ($p < 0.001$).

Table 3 depicts a significant value of higher glycaemic gap in massive pulmonary embolism compared with sub-massive and non-massive subtypes ($p < 0.001$).

Validity of glycaemic gap as a predictor of mortality in diabetic patients with pulmonary embolism was shown in Table 4. At a cut-off value of greater than or equal to 73, sensitivity, specificity, positive predictive value, and negative predictive value were 100, 83, 22, and 100%, respectively.

Table 1: Comparability among survivors and non- survivors considering distinct variables.

Variables	Survivors (n=136) [n (%)]	Non-survivors (n=26) [n (%)]	p
Age (years)	49.2±3.2	53.3±3.4	0.002
PESI	74.6±14.3	102±21.7	0.001
LOS (days)	4.1±0.23	4.9±0.29	0.001
BMI (kg/m ²)	26.8±2.1	28.9±2.7	0.32
Gender			
Male	73 (53.6)	9 (34.6)	0.04
Female	63 (46.3)	17 (65.3)	
Habit (Smoking)			
Yes	79 (58.0)	12 (46.1)	0.39
No	57 (41.9)	6 (23.0)	
Comorbidities			
Chronic Pulmonary disease	23(16.9)	3 (11.5)	0.28
Chronic heart Disease	19 (13.9)	4 (15.3)	
Chronic renal Disease	29 (21.3)	2 (7.6)	
Chronic hepatic Disease	17(12.5)	3 (11.5)	
Neuromuscular disease	16 (11.7)	1 (3.8)	

LOS- length of hospital stays; PESI- pulmonary embolism severity index

Table 2: Readings of glycaemic gap in different clinical consequences of the enlisted diabetic patients with pulmonary embolism

Outcomes	n (%)	Glycaemic gap	p
Non-survivors	26 (16.0)	109.4±24.1	<0.001
Survivors	136 (83.9)	47.3±12.6	
With clinical deterioration	13 (8.0)	104.02±12.3	<0.001
Without clinical deterioration	149 (91.9)	47.2±12.3	
Need ICU	21 (12.8)	106.2±23.7	<0.001
Not need ICU	141 (86.5)	43.1±14.8	

Table 3: Glycaemic gap in different types of pulmonary embolism

Pulmonary embolism type	n (%)	Glycaemic gap	p
Non-massive	93 (57.4)	37.3±9.3	<0.001
Sub-massive	46 (28.3)	83.1±11.6	
Massive	23 (14.1)	107±13.9	

Table 4: Validity of glycaemic gap as mortality predictor

Variables	Glycaemic gap ≥73
Sensitivity (%)	100
Specificity (%)	83
PPV (%)	22
NPV (%)	100
95% CI	0.943–0.98
AUC	0.95
P	<0.001

AUC- area under the curve; CI- confidence interval; NPV- negative predictive value; PPV- positive predictive value

Table 5: Predictors associated with mortality using logistic regression model

Variables	OR	95% CI	p value
Glycaemic gap	1.02	1.01–1.07	0.043
PESI	1.03	1.03–1.02	<0.001
LOS (days)	0.46	0.82–1.7	0.37
Age	0.87	0.87–1.2	0.13

CI- confidence interval; LOS- length of hospital stays; OR- odds ratio; PESI- pulmonary embolism severity index

Multivariate logistic regression for identifying the potential predictors of mortality is shown in Table 5, and two substantiate independent predictors are PESI ($p < 0.001$) and glycemic gap ($p = 0.043$) which can be preferably use in future in predicting the survival of the patient.

4. Discussion

Patients suffering from pulmonary embolism manifest variable clinical presentation ranging from completely asymptomatic to sudden death due to cardiac arrest. Despite the fact that in modern day with continuous advancement of technology even in diagnosis and treatment of pulmonary embolism which no doubt improved the treatment outcome but still the mortality rate remains high which is a matter of concern. According to the recent data, more than 10% of the nosocomial demises are associated with pulmonary embolism.^{6–8} Another statistics revealed that about 50% mortality is observed in hypotensive patients suffering from pulmonary embolism admitted to the hospital. During hospitalization, round about 90% of patients suffering from acute pulmonary embolism (APE) are having blood pressure in the normal range, however short-term mortality is extensively inconstant and varied from less than 1% to 15%.⁹

Along with the diagnosis of pulmonary embolism, consecutively it is mandatory to evaluate the prognostication of risk stratification and a definite therapeutic judgement. Previous proclaimed reports have suggested complex scores or indices and diversified biomarkers to identify the risk stratification in APE patients, which are pragmatically strenuous to evaluate in an emergency setting or situation, the reason being it will require additional expertise along with the financial burden to patient.^{10,11} Looking into the similar facts specially in developing countries with limited resources, a simpler inexpensive screening tool is desired which can work in ordinary clinical setting with comprehensible indices.^{12,13} Various prognostic models are available and among them few can definitely recommended for identifying risk stratification in acute pulmonary embolism beside the fact that many of them have limited use in routine clinical practice. SIH has been identified as self reliant factor which is associated with an increased risk of mortality in case of critical illness including pulmonary embolism in non-diabetic patients. Although, in diabetic patients the exact role of SIH is debatable and unclear.^{14,15}

Present study revealed a significant finding that is a positive correlation between glycemic gap and the severity of pulmonary embolism. On comparison, non- survivors had advanced age group (53.3 ± 3.4 vs. 49.2 ± 3.2 , $p = 0.002$), higher PESI (102 ± 21.7 vs. 74.6 ± 14.3 , $p < 0.001$) and prolonged hospital stay (4.9 ± 0.29 days vs. 4.1 ± 0.23 days, $p < 0.001$) and the difference was statistically significant. Whereas other parameters like body mass index (BMI), gender distribution, habits (particularly smoking) and

associated comorbidities depicts no significant difference between both the groups. Peculiarly, a highly significant difference was observed in relation to the glycemic gap between non- survivors and survivors (37.3 ± 9.3 vs. 83.1 ± 11.6 , $p < 0.001$), patients with and without clinical deterioration (104.02 ± 12.3 vs. 47.2 ± 12.3 , $p < 0.001$), and patients who were and were not in-need of ICU admission (43.1 ± 14.8 vs. 106.2 ± 23.7 , $p < 0.001$). Considering different subtypes of pulmonary embolism significantly higher glycemic gap was derived in patients with massive pulmonary embolism as compared to sub-massive and non-massive types (107 ± 13.9 , 83.1 ± 9.6 , and 37.3 ± 9.3 , respectively, $p < 0.001$).

The current study depicts the validity of glycemic gap (at a cut-off value of equal to or greater than 73) as a predictor of mortality in diabetic patients with pulmonary embolism which divulged into the fact that at this cut off of glycemic gap, the values obtained for sensitivity, specificity, positive predictive value, and negative predictive value were 100, 83, 22, and 100%, respectively. Our study identified valuable two independent predictors of mortality using multivariate logistic regression; those were PESI ($p < 0.001$) and glycemic gap ($p = 0.043$). A recent study done by Petrauskiene V et al.,¹⁶ also revealed that patients with diabetes mellitus hospitalized for venous thromboembolism, had markedly elevated blood glucose at the time of admission and there was significant correlation with increased mortality. On the other hand, there is difference in the results between the study of Carl GFet al.,¹⁷ and present study related to diabetic patients which can be explained by that in our study, glycemic gap was used instead of depending on hyperglycaemia at the time of admission to avoid the influence of chronic hyperglycaemia on the admission hyperglycaemia in diabetics. Similar to the present study, few previous studies also confirmed that unfavourable prognosis in diabetics with pyogenic hepatic abscess was associated with an elevated glycaemic gap (> 72 mg/dl).¹⁸

Present study came out with the overall mortality rate of 16%, which is almost comparable with the previous studies related to pulmonary embolism.¹⁹ Additionally, the result of current study revealed 8% of pulmonary embolism patients showed clinical and this is in accordance with the study done by Chung et al., which depicts the 30-day complication rate of patients with pulmonary embolism as 9.2%.²⁰ To the best of our knowledge no prospective study has been conducted so far to evaluate the efficiency of the factor or biomarker glycemic gap in diabetic patients with pulmonary embolism, which further gives strength and validation to this present prospective study in this regard.

Considering few drawbacks of the current study like the influence of glycemic control during hospitalization was not assigned, which might have affected the consequences and end results. Further research should be done in future

with increased number of patients to validate the role of glycemic gap as a biomarker in defining the intensity and consequences of pulmonary embolism in diabetic patients.

5. Conclusions

The uplifted level of glycemic gap between serum glucose levels upon admission and the HbA1c-derived average glucose manifesting the strong correlation to the increase in rigourness of disease along with rate of mortality in diabetic patients with pulmonary embolism. Therefore, we propose here to use glycemic gap as a biomarker in predicting the severity and prognosis of pulmonary embolism.

6. Source of Funding

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7. Conflict of Interest

Authors has no conflict of interest whatsoever.

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