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The impact of hyperosmolarity on long-term outcome in patients presenting with severe hyperglycemic crisis: a population based study

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Abstract

Aims: We aimed to compare characteristics of patients with hyperglycemic hyperosmolar state (HHS) and patients with severe hyperglycemia without the signs of hyperosmolarity and ketoacidosis; to analyze long-term all-cause mortality and potential prognostic factors.

Methods: The studied population included 261,749 adults. HHS was diagnosed in patients with plasma glucose >33.0 mmol/L, ketonuria <1+, and serum osmolarity >320 mmol/L. Patients with plasma glucose >33.0 mmol/L, ketonuria <1+ and serum osmolarity <320 mmol/L were used as controls (nHHS).

Results: During the 5-year period, we observed 68 episodes of HHS in 66 patients and 51 patients with nHHS. Patients with HHS were significantly older, had lower BMI, higher serum C-reactive protein and used diuretics and benzodiazepines more frequently. Mortality rates one, three and 12 months after admission were 19.0%, 32.1% and 35.7% in the HHS group, and 4.8%, 6.3% and 9.4% in the nHHS group ($P<0.001$). However, after adjustment for patient age, these differences were not statistically significant. In multivariate Cox regression in HHS group, mortality was positively associated with age, male gender, leukocyte count, amylase, presence of dyspnea and somnolence, and the use of benzodiazepines, ACE inhibitors and sulphonylureas, while it was inversely associated with plasma glucose, bicarbonate, and the use of thiazides and statins. A nomogram derived from these variables had an accuracy of 89% in predicting lethal outcome.

Conclusions: Infection, use of diuretics and benzodiazepines may be important precipitating factors of HHS. Prospective clinical trials are mandatory to analyze the safety of ACE-inhibitors and benzodiazepines in elderly patients with diabetes.

Key words: Diabetes mellitus type 2, hyperglycemic hyperosmolar state, mortality, angiotensin-converting enzyme inhibitors, benzodiazepines; precipitating factors

1. Introduction

Hyperglycemic hyperosmolar state (HHS) is a life-threatening acute hyperglycemic complication that mostly occurs in elderly patients with type 2 diabetes mellitus (DM) [1]. However, there is some overlap with diabetic ketoacidosis in adults [2], and it can occur in pediatric patients with type 2 diabetes [3]. The exact pathophysiology is unknown, but severe insulin resistance and underlying chronic kidney disease play an important role [4]. The true incidence of HHS is unknown because population-based studies have not been conducted. Based on data on annual discharges of HHS in the United States, it is estimated that HHS affects approximately 1 of 500 patients with DM and the overall incidence of HHS is less than 1 case per 1000 person-years [5]. Previous studies have reported that HHS occurs more commonly in elderly female patients, with the majority of patients having newly diagnosed DM and infection as the leading precipitating factor [1,2,6–9]. Inpatient mortality rates are reported to be between 10-40% [1,2,6–9].

Studies have found that prognostic factors for HHS include age, altered mental status, the presence of cardiovascular comorbidities, serum blood nitrogen, sodium, pH, and bicarbonates [1,2,6–11]. However, the majority of studies analyzed only inpatient mortality, and data on the prognostic accuracy of these variables are lacking.

The aim of this population-based, case-control study was to: compare the characteristics of patients with HHS and patients with severe hyperglycemia without signs of hyperosmolarity and ketoacidosis; analyze long-term all-cause mortality and detect potential prognostic factors.

2. Methods

2.1. Study protocol

This was a population-based, cross-sectional, cohort study performed in the emergency department of a teaching hospital. We reviewed electronic charts from all patients with plasma glucose (PG) >33.0 mmol/L at admission between January 1st 2010 and December 31st 2014. HHS was defined as PG >33.0 mmol/L, ketonuria <1+ and serum osmolarity >320 mmol/L. Patients with PG >33.0 mmol/L, ketonuria <1+ and serum osmolarity <320 mmol/L were used as controls (nHHS).

We analyzed the following parameters: general anthropometric characteristics (age, gender, hospitalization and place of residency); signs and symptoms (weight loss, polyuria and polydipsia, increased body temperature, vomiting, abdominal pain, dyspnea, mental status changes and electrocardiograms); medication (angiotensin-converting-enzyme [ACE] inhibitors, calcium channel antagonists, beta-blockers, furosemide, thiazide diuretics, statins, antipsychotics, benzodiazepines, sulfonylureas, metformin, insulin and alcohol consumption). Diabetes-specific data including body mass index (BMI) and duration of diabetes was obtained by searching other institutional electronic registries. Medical doctors were responsible for reviewing all electronic charts. All-cause mortality data were obtained from the Croatian Department of Public Health.

2.2. Statistical analyses

Patient characteristics were assessed using descriptive statistics presented as a mean with standard deviation. Continuous variables were compared with Mann-Whitney test and

categorical variables with Fisher exact test. Cox proportional hazard models were used to analyze the link between patient characteristics and mortality. Backward conditional stepwise approach was used to determine variables independently associated with survival. Stepwise conditional backward Cox regression was performed separately in each group of variables: signs and symptoms (weight loss, polyuria and polydipsia, increased body temperature, vomiting, abdominal pain, dyspnea, mental status and electrocardiograms); general anthropometric characteristics and laboratory findings (age, gender, place of residency and laboratory findings); medication (ACE inhibitors, calcium channel antagonists, beta-blockers, furosemide, thiazide diuretics, statins, antipsychotics, benzodiazepines, sulfonylureas, metformin, insulin and alcohol consumption). A nomogram was constructed in the form of a regression equation based on unstandardized correlation coefficients derived from the final step of stepwise conditional backward Cox regression. Receiver operating characteristic (ROC) analysis was performed in order to determine the sensitivity, specificity and positive likelihood ratio of the nomogram in predicting all-cause mortality. P values <0.05 were considered significant. The statistical analysis was done using SPSS Version 20.0.

3. Results

3.1. Patient characteristics

A total of 68 episodes of HHS occurred in 66 patients. HHS was rare in patients younger than 60 years, although three patients younger than 60 were diagnosed with HHS.

Patients with HHS had a median age of 79 (74-86) and 44.1% (30/68) were males. When compared with patients with nHHS, patients with HHS were significantly older and had lower BMIs (Table 1). The proportion of patients with newly diagnosed DM was lower in the HHS

group. Consequently, a greater proportion of patients with HHS used oral antidiabetic agents and insulin. As expected, patients with HHS had higher serum glucose, blood nitrogen, creatinine, sodium, and lower base excess. Although patients with HHS had higher rates of altered mental status, altered mental status occurred in only 26.5% of patients. Patients with HHS had higher rates of ECG abnormalities, while those with nHHS reported polyuria and weight loss more frequently. Interestingly, more patients in the HHS group used benzodiazepines, which may be a precipitating factor in some patients (Table 1).

3.2. Mortality

After a median follow-up of 24.0 (1.3–36.0) months, 31 patients (46.9%) in the HHS group died. Mortality rates one, three and 12 months after admission were 19.0%, 32.1% and 35.7% in the HHS group, and 4.8%, 6.3% and 9.4% in the NHHS group, respectively ($P<0.001$ for all comparisons). Patients with HHS had a higher chance of lethal outcome (HR 2.35, 95% CI 1.23–4.50, $P=0.010$), especially within the first three months after admission (Figure 1). However, after adjustment for patient age, these differences were not statistically significant (HR 1.77, 95% CI 0.89–3.51, $P=0.103$).

In the HHS group, all-cause mortality was positively associated with age, male gender, leukocyte count, amylase, presence of dyspnea and somnolence, and the use of benzodiazepines, ACE inhibitors and sulphonylureas. On the other hand, it was inversely associated with plasma glucose, bicarbonate, and the use of thiazides and statins. In the nHHS group, all-cause mortality was positively associated with blood nitrogen, sodium, base excess, and the use of sulphonylureas, while it was inversely associated with age, hemoglobin, bicarbonate, and CRP (Table 2).

Therefore, we constructed a nomogram for patients with HHS in the form of a regression equation: age × 0.079 + male gender × 0.945 – PG × 0.058 + leukocytes × 0.058 + serum amylase × 0.003 – serum bicarbonates × 0.094 - thiazides × 2.793 - statins × 1.910 + benzodiazepines × 1.350 + ACE inhibitors × 2.483 + sulphonylureas × 1.891 + dyspnea × 1.191. The nomogram had an area under the curve (AUC) of 0.893 (95% CI 0.767–1.000) in predicting mortality (Figure 2). A score of >4.03 had a sensitivity of 91.7% (61.5–99.8) and a specificity of 78.6% (49.2–95.3), with a positive predictive value of 4.3 (1.5–11.8).

4. Discussion

Our study revealed several new and interesting points that we would like to discuss. In our predominantly Caucasian population, HHS was more common in males, which is similar to reports from an Asian population [7]. When compared to patients with nHHS, the prevalence of newly diagnosed DM was substantially lower in patients with HHS, which is contradictory to previous studies [11]. We did not perform a specific analysis of precipitating causes of HHS for several reasons. First of all, the diagnosis of infection is hard to make in this subgroup of patients. Elderly patients may often be afebrile, even in the presence of acute infection. Moreover, leukocyte count in patients with HHS may be increased due to dehydration and hyperosmolarity. CRP levels may also be increased due to chronic kidney disease, which is also prevalent in these patients [12]. Moreover, approximately 25% of patients with HHS had altered mental status; therefore, information on therapy adherence may be unreliable.

Our study was the first to analyze medication use in patients with HHS. The prevalence of furosemide and benzodiazepine use was substantially higher in patients with HHS. This is an important observation because both may be predisposing factors for HHS. A few case reports of HHS precipitated by diuretic use have been described [13]. Although antipsychotics and

antidepressants are well known precipitators of both HHS and diabetic ketoacidosis [14], little is known about the role of benzodiazepines in these clinical entities. Benzodiazepines are associated with a number of adverse effects including daytime sedation and slowed psychomotor performance [15], both of which may predispose to dehydration, progression of kidney disease, and eventually HHS.

Mortality rates in our study were exceedingly high, especially within the first three months after admission. Although the overall differences in mortality were not statistically significant after adjustment for age, these differences were different within the first year of follow-up. As reported in previous studies, advanced age, male gender, high glucose, high leukocyte count, low bicarbonates, and altered mental status were associated with increased mortality. In addition to the previously established prognostic factors, we found that high serum amylase and the presence of dyspnea at admission were independently associated with mortality. A nonspecific increase in serum amylase is often seen in patients with diabetic ketoacidosis and correlates well with the rate of dehydration, hyperosmolarity, and acidosis [16]. However, an independent association between serum amylase and mortality is a novel finding, which needs to be validated in future studies. The presence of dyspnea may correlate with metabolic acidosis and renal and heart failure, which are all well-known adverse prognostic factors. In our opinion, the most important finding of our study is the association between thiazide and statin use with lower mortality and the association between benzodiazepines, ACE inhibitors, and sulphonylureas with increased mortality. Although thiazide diuretics are associated with glucose intolerance and increase the risk for diabetes [17], they reduce cardiovascular mortality in patients with diabetes [18]. In our study, a history of thiazide use was associated with an 80% reduction in all-cause mortality. The link between statins and decreased mortality is well known, and in our study statin use was associated

with a 20% reduction in all-cause mortality. The fact that benzodiazepines use was associated with a 4-fold increase in mortality in patients with HHS is a novel finding. This can be explained by the previously mentioned daytime sedation and slowed psychomotor performance, both of which can predispose to dehydration and progression of kidney disease. Previous studies have found increased mortality in sulphonylurea users[19], so the fact that their use in patients with HHS was associated with a 6-fold increase in all-cause mortality could be expected. The most striking finding of our study was the 12-fold increase in all-cause mortality in patients with HHS that used ACE inhibitors. ACE inhibitors decrease overall mortality in patients with diabetes [20]. However, ACE inhibitors may induce acute renal failure in some patients [21]. A study by Shin et al. analyzed urinary atrial natriuretic peptide-like immunoreactivity and plasma atrial natriuretic peptide concentration in patients with hyperosmolar-hyperglycemic nonketotic syndrome (HHNS). The study showed that urinary atrial natriuretic peptide-like immunoreactivity was significantly increased, whereas plasma atrial natriuretic peptide concentration was decreased in the face of raised plasma renin activity in HHNS patients. This study indicated that renal atrial natriuretic peptide-like immunoreactivity substances and cardiac atrial natriuretic peptide may have different responsiveness in diabetic patients with HHS [22]. These findings may explain why ACE inhibitors exhibit different effects in patients with HHS, which was not observed in patients nHHS.

In the end, we would like to emphasize that our study is the first to report the prognostic accuracy of a nomogram in patients with HHS. Our nomogram had 90% accuracy in predicting mortality, which could be useful in clinical practice. However, future validation studies are needed.

In conclusion, patients with HHS have higher CRP levels and leukocyte count suggesting that

infection is a common precipitating factor. The increased use of diuretics and benzodiazepines among elderly patients with DM may predispose them to develop HHS. We found that thiazides and statins were associated with decreased mortality, and benzodiazepines, ACE inhibitors and sulphonylureas were associated with increased mortality. Prospective clinical trials are mandatory to analyze the safety of these agents in elderly patients with diabetes.

Conflict of interest: None.

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Ethical standard: The study was approved by the local Institutional Review Board. Human and animal rights. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1. Characteristics of the study population divided based on the presence of hyperglycemic hyperosmolar syndrome (HHS)

	nHHS (A) N=51	HHS (B) N=68
Age (years)	68 (55-80)	79 (74-86) [A]
Male gender % (n)	49.0 (25)	44.1 (30)
Duration of DM (years)	10.0 (0.-19.0)	10.4 (7.0-15.0)
BMI (kg/m^2)	28.1 (23.6-31.1)	25.6 (23.0-28.3) [A]
Rural residency % (n)	41.2 (21)	42.4 (28)
Newly diagnosed DM % (n)	37.5 (18)	8.2 (5) [A]
Glucose (mmol/L)	36.8 (34.6-39.9)	39.9 (36.1-46.5) [A]
Leukocytes (10^9/L)	9.7 (7.5-12.6)	12.9 (8.8-18.2) [A]
Hemoglobin (g/L)	137.0 (126.0-144.0)	135.0 (126.0-147.0)
Serum nitrogen (mmol/L)	9.9 (7.9-13.6)	22.1 (13.4-32,4) [A]
Creatinin (μmol/L)	129.0 (107.0-165.0)	201.5 (157.0-250.5) [A]
Sodium (mmol/L)	128.0 (123.0-131.0)	133.0 (131.0-138.0) [A]
Potassium (mmol/L)	4.5 (4.0-4.9)	4.5 (4.2-5.2)
Amylase (U/L)	38.5 (25.5-57.5)	46.0 (26.0-80.0)
CRP (mg/L)	14.5 (4.3-101.9)	39.3 (11.6-117.5)
AST (U/L)	18.5 (14.0-30.0)	19.0 (14.5-32.5)
ALT (U/L)	24.0 (15.0-41.0)	20.5 (14.0-34.0)
Capillary blood Ph	7.42 (7.37-7.45)	7.40 (7.32-7.43)
Base excess (mmol/L)	-1.7 (-6.1-1.8)	-4.8 (-9.9-(-0.3)) [A]
Bicarbonates (mmol/L)	20.7 (16.5-22.9)	17.7 (14.7-22.2)
Osmolarity (mmol/L)	312.5 (306.9-316.6)	336.1 (325.8-363.3) [A]
Abdominal pain % (n)	9.8 (5)	5.9 (4)
Vomiting % (n)	3.9 (2)	13.2 (9)
Dyspnea % (n)	9.8 (5)	19.1 (13)
Febrile % (n)	3.9 (2)	16.1 (11)
Polyuria % (n)	45.1 (23)	22.1 (15) [A]

Weight loss % (n)	15.7 (8)	2.9 (2) [A]
Somnolence % (n)	0.0 (0)	16.2 (11) [A]
Sopor % (n)	2.0 (1)	8.8 (6)
Coma % (n)	2.0 (1)	1.5 (1)
Arrhitmia % (n)	17.6 (9)	39.7 (27) [A]
Thiazide diuretic % (n)	9.8 (5)	23.5 (16)
Fursemide % (n)	19.6 (10)	35.3 (24)
Antipsychotics % (n)	9.8 (5)	11.8 (8)
Benzodiazepines % (n)	3.9 (2)	20.6 (14) [A]
Betablockers % (n)	27.5 (14)	44.0 (30)
ACE inhibitors % (n)	33.3 (17)	51.5 (35)
Insulin therapy % (n)	9.8 (5)	32.4 (22) [A]
Metformin % (n)	5.9 (3)	22.1 (15) [A]
Sulphonylureas % (n)	13.7 (7)	42.6 (29) [A]
Alcohol % (n)	9.8 (5)	7.4 (5)

A – significant when compared with patients with nHHS

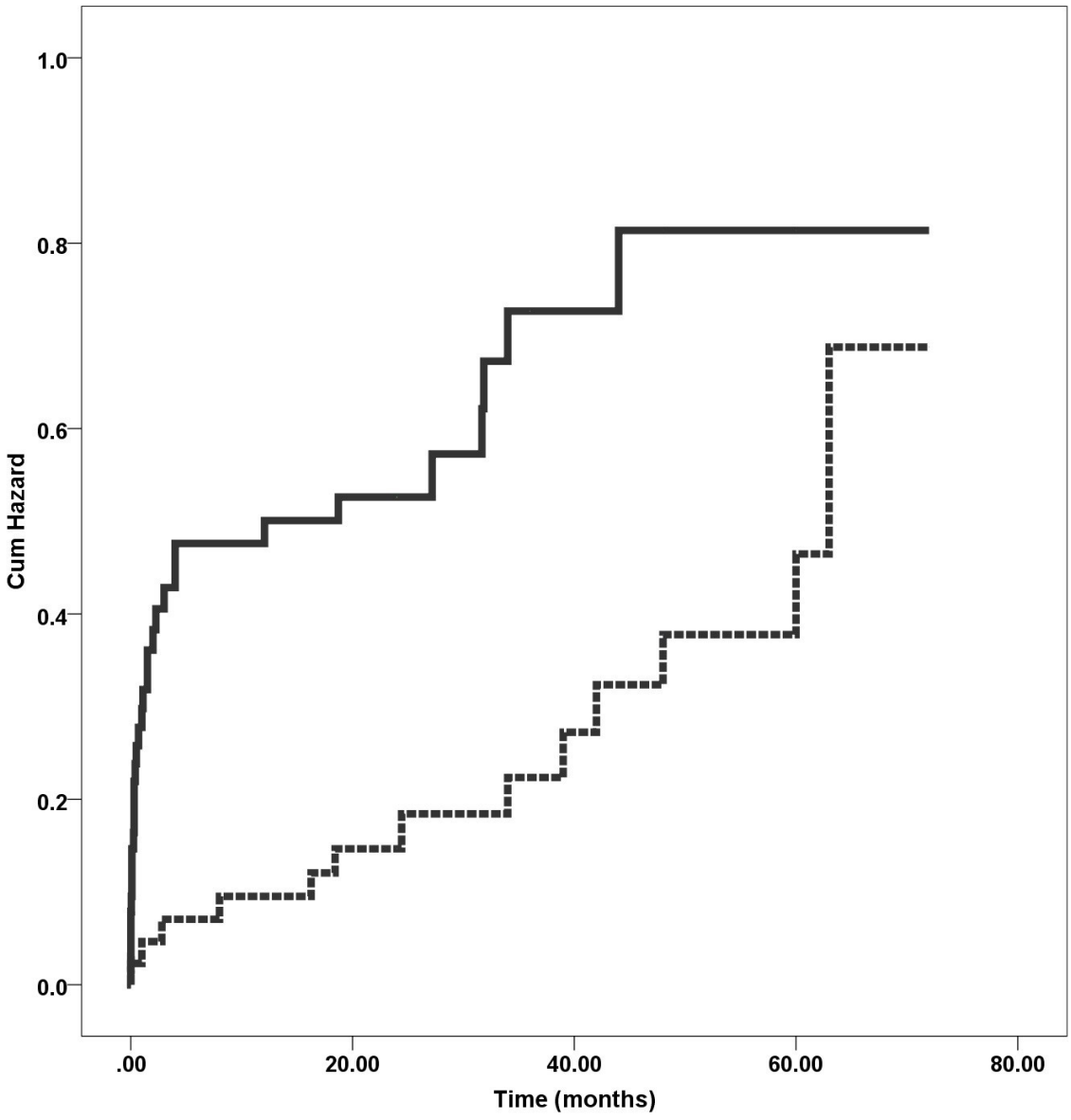
Table 2. Results of stepwise conditional backward Cox regression in patients with HHS and nHHS, showing independent predictors of all-cause mortality.

	B	SE	HR	95% CI for HR		P
HHS						
Age	.079	.023	1.082	1.034	1.132	.001
Male gender	.945	.457	2.573	1.050	6.307	.039
Plasma glucose	-.058	.026	.944	.896	.994	.028
Leukocyte count	.058	.028	1.059	1.003	1.119	.037
Amylase	.003	.001	1.003	1.001	1.006	.016
Bicarbonates	-.094	.035	.911	.851	.974	.007
Dyspnea	1.191	.489	3.291	1.262	8.581	.015
Somnolence	.826	.291	2.284	1.290	4.043	.005
Thiazides	-2.793	.762	.061	.014	.272	.000
Statins	-1.910	.872	.148	.027	.818	.028
Benzodiazepines	1.350	.649	3.859	1.081	13.776	.038
ACE inhibitors	2.483	.607	11.980	3.647	39.349	.000
Sulphonylureas	1.891	.543	6.623	2.285	19.198	.000
nHHS						
Age	-.117	.056	.890	.797	.992	.036
Hemoglobin	-.113	.035	.893	.834	.956	.001
Serum nitrogen	.748	.275	2.112	1.231	3.622	.007
Sodium	.990	.328	2.693	1.417	5.117	.002
CRP	-.018	.009	.982	.965	.999	.043
Base excess	.912	.342	2.491	1.274	4.868	.008
Bicarbonates	-1.374	.492	.253	.096	.664	.005
Sulphonylureas	2.331	.983	10.287	1.497	70.682	.018

B – unstandardised correlation coefficient; SE – standard error; HR – hazard ratio; CI – confidence interval;

Figure 1. Kaplan-Meier curves showing cumulative hazard between patients with hypergylcemic hyperosmolar syndrom (full line) and those with severe hyperglycemia without the signs of hyperosmolarity (interrupted line).

Figure 2. ROC curve showing the diagnostic performance of nomogram in predicting all-cause mortality in patients with hyperglycemic hyperosmolar syndrome.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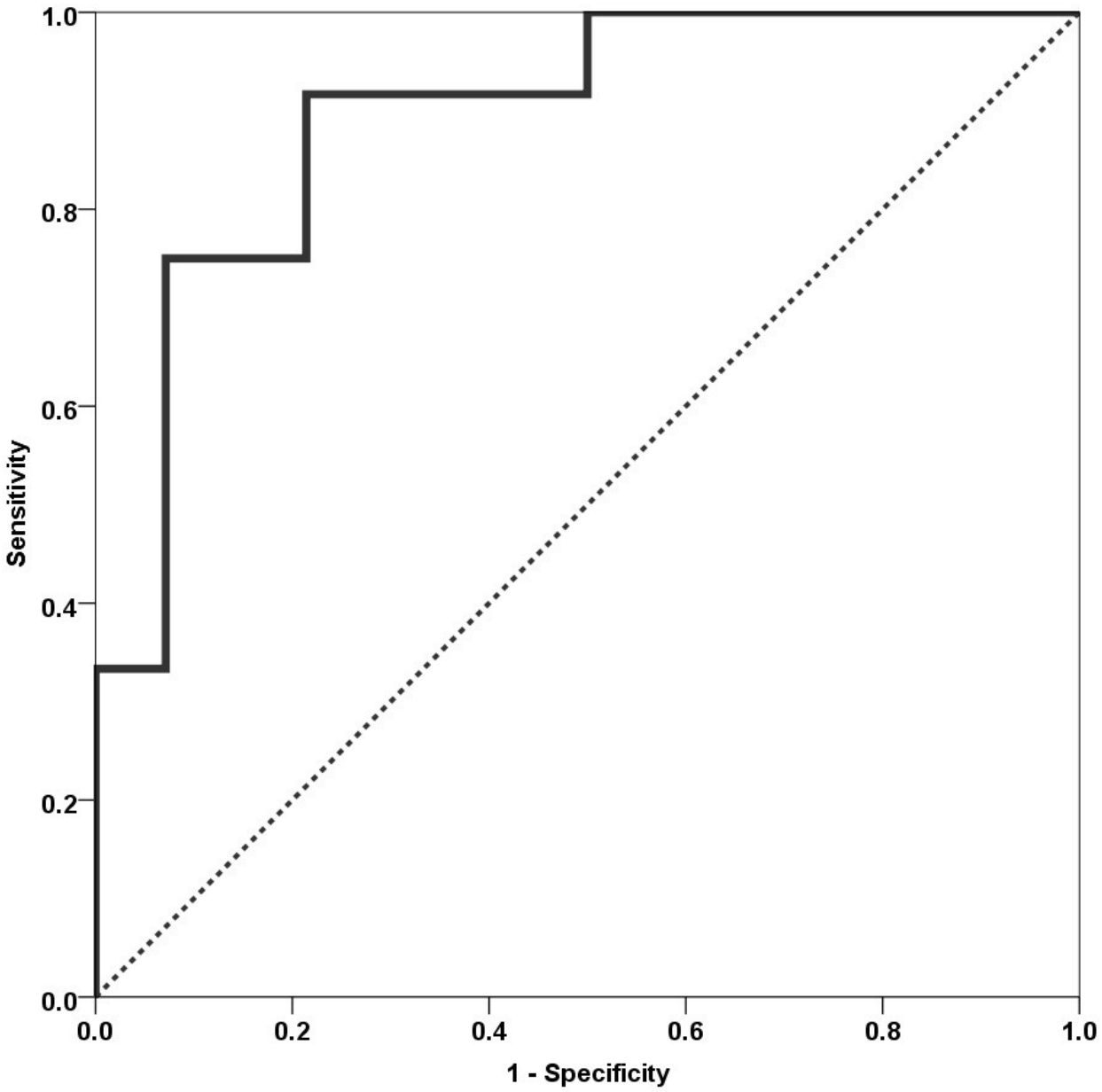
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